FILE 'MEDLINE' ENTERED AT 22:17:20 ON 17 SEP 2004

FILE 'HCAPLUS' ENTERED AT 22:17:20 ON 17 SEP 2004

=> s l1 and (gemcitabin? or paclitax? or docetax? or cisplatin? or carboplatin? or etoposid? or adriamycin? or topotecan? or CPT(w)(II or 11) or capecitabin? or radiat?)
L9 16 L1 AND (GEMCITABIN? OR PACLITAX? OR DOCETAX? OR CISPLATIN? OR CARBOPLATIN? OR ETOPOSID? OR ADRIAMYCIN? OR TOPOTECAN? OR CPT(W)(II OR 11) OR CAPECITABIN? OR RADIAT?)

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10 13 DUP REM L9 (3 DUPLICATES REMOVED)

=> d l10 abs cbib kwic hitrn 1-13

L10 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
AB The invention describes administration of an irreversible tyrosine kinase inhibitor such as CI-1033 in combination with one or more other antineoplastic agent(s), or ionizing **radiation** is synergistic for treating cancer.
2004:142967 Document Number 140:175126 Therapeutic combinations of erb b kinase inhibitors and antineoplastic therapies. Elliott, William Leon; Fry, David William (Warner-Lambert Company Llc, USA). PCT Int. Appl. WO 2004014386 A1 20040219, 40 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-IB3388 20030728. PRIORITY: US 2002-PV401705 20020807; US 2003-PV462247 20030411.
AB . . . of an irreversible tyrosine kinase inhibitor such as CI-1033 in combination with one or more other antineoplastic agent(s), or ionizing **radiation** is synergistic for treating cancer.
ST erb B kinase inhibitor antineoplastic antitumor ionizing **radiation**
IT Antitumor agents
Bladder, neoplasm
Esophagus, neoplasm
Head, neoplasm
Human
Ionizing **radiation**
Mammary gland, neoplasm
Melanoma
Multiple myeloma
Neoplasm
Neuroglia, neoplasm
Ovary, neoplasm
Pancreas, neoplasm
Prostate gland, neoplasm

Psoriasis
Radiotherapy
Sarcoma
Thyroid gland, neoplasm
(therapeutic combinations of erb B kinase inhibitors and antineoplastic therapies)

IT 33069-62-4, **Paclitaxel**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Taxol; therapeutic combinations of erb B kinase inhibitors and antineoplastic therapies)

IT 114977-28-5, **Docetaxel**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Taxotere; therapeutic combinations of erb B kinase inhibitors and antineoplastic therapies)

IT 15663-27-1, **Cisplatin** 25316-40-9, **Adriamycin**
33419-42-0, **Etoposide** 41575-94-4, **Carboplatin**
95058-81-4, **Gemcitabine** 100286-90-6, **CPT-11**
123948-87-8, **Topotecan** 154361-50-9, **Capecitabine**
267243-28-7 **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic combinations of erb B kinase inhibitors and antineoplastic therapies)

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic combinations of erb B kinase inhibitors and antineoplastic therapies)

L10 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

AB Methods for treating cancer are described here. The methods include administering to an HIV-neg. patient an m-calpain inhibitor such as ritonavir. Ritonavir or other m-calpain inhibitors can also be co-administered with other therapeutic agents such as a Cox-2 inhibitor, a taxane, or a proteasome inhibitor. Methods for determining whether a patient will respond to a particular method of treatment are also described herein.

2004:100947 Document Number 140:139486 Method of treating cancer. Potter, David A. (Advanced Research & Technology Institute at Indiana University, USA). PCT Int. Appl. WO 2004010937 A2 20040205, 69 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US23437 20030728. PRIORITY: US 2002-PV399573 20020726.

IT 50-07-7, Mitomycin-c 50-18-0, Cyclophosphamide 50-24-8, Prednisolone
50-76-0, Dactinomycin 51-21-8, 5-Fluorouracil 57-22-7, Vincristine
58-05-9, Leucovorin 59-05-2, Methotrexate 147-94-4, Cytarabine
148-82-3, Melphalan 564-25-0, Doxycycline 671-16-9, Procarbazine
865-21-4, Vinblastine 3778-73-2, Ifosfamide 4291-63-8, 2-CDA

10540-29-1, Tamoxifen 11056-06-7, Bleomycin 13311-84-7, Flutamide 15663-27-1, **Cisplatin** 18883-66-4, Streptozocin 20830-81-3, Daunorubicin 21679-14-1, Fludarabine 29767-20-2, Teniposide 33069-62-4, **Paclitaxel** 33419-42-0, **Etoposide** 41575-94-4, **Carboplatin** 53714-56-0, Leuprolide 56420-45-2, Epirubicin 65271-80-9, Mitoxantrone 65277-42-1, Ketoconazole 71486-22-1, Vinorelbine 84449-90-1, Raloxifene 89778-26-7, Toremifene 97682-44-5, Irinotecan 112809-51-5, Letrozole 114977-28-5, **Docetaxel** 120511-73-1 126775-97-1, Campath 127779-20-8, Saquinavir 129453-61-8, Fulvestrant 150378-17-9 155213-67-5 159878-27-0 161814-49-9 169590-42-5, Celecoxib 174722-31-7, Rituximab 179324-69-7, VELCADE 183319-69-9, Tarceva 184475-35-2, Iressa 192725-17-0 205923-56-4, C225 231277-92-2, GW 572016 257933-82-7, EKB569 **289499-45-2**, CI-1033 339177-26-3, ABX-EGF
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treating cancer)

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treating cancer)

L10 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

AB The present invention relates to a novel method of preventing and/or treating neoplasia disorders in a subject that is in need of such prevention or treatment by administering to the subject at least one COX-2 inhibitor in combination with an EGF receptor antagonist. Compns., pharmaceutical compns. and kits are also described.

2004:533970 Document Number 141:65088 Methods and compositions for the prevention or treatment of neoplasia comprising a COX-2 inhibitor in combination with an epidermal growth factor receptor antagonist. Masferrer, Jaime (Pharmacia Corporation, USA). U.S. Pat. Appl. Publ. US 2004127470 A1 20040701, 103 pp., Cont.-in-part of U.S. Ser. Number 470,951. (English). CODEN: USXXCO. APPLICATION: US 2003-651916 20030829. PRIORITY: US 1998-PV113786 19981223; US 1999-470951 19991222.

IT 33069-62-4, **Paclitaxel**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(COX-2 inhibitor and EGFR antagonist in combination with; COX-2 inhibitor in combination with epidermal growth factor receptor antagonist for prevention or treatment of neoplasia)

IT 95-16-9D, Benzothiazole, compds. 100-42-5D, Styrene, substituted 253-66-7D, Cinnoline, derivs. 253-82-7D, Quinazoline, compds. 446-72-0, Genistein 446-72-0D, Genistein, conjugates with epidermal growth factor 458-37-7, Curcumin 15018-66-3D, 4-Aminoquinazoline, compds. 34157-83-0, Celastrol 34923-95-0D, compds. 37270-94-3, Platelet factor 4 62229-50-9D, EGF, fusion proteins with toxin 75706-12-6, SU-101 80497-65-0, Muellerian-inhibiting hormone 104326-05-8, BBR 1611 117147-70-3, Amphiregulin 118409-60-2, RG-50864 129298-91-5, AGM-1470 134615-37-5, Reveromycin A 134633-29-7, Tecogalan sodium 138147-78-1, RC-3095 138989-57-8, RG-14620 140674-76-6, AG-957 140674-79-9, AG 514 145588-13-2, BE 23372M 145588-13-2D, BE 23372M, derivs. 145915-60-2, CGP 53353 146426-40-6, Flavopiridol 147159-51-1, TT-232 149286-90-8, RG-13022 150779-71-8, SDZ-LAP-977 150977-36-9, Bromelain 151013-48-8, AG-568 152459-94-4, CGP-53716 152459-95-5 153436-53-4, AG 1478 153436-54-5, SU 5271 153436-54-5D, analogs 153436-70-5, ZM 105180 154387-41-4, NSC 675967

156177-59-2, CEP-751 157168-02-0, CGP-52411 162382-68-5, RC-3940-II
164003-59-2, VRCTC-310 171179-06-9, PD 158780 173458-56-5, CGP-59326
176915-62-1, CGP-62706 179343-17-0, PD-089828 180288-69-1, Trastuzumab
183319-69-9 183321-74-6, Erlotinib 183488-70-2, CEP-2563
184475-35-2, ZD-1839 185077-23-0, PI 88 186519-23-3D, compds.
187724-61-4, PKI-166 194423-15-9, PD-168393 196612-93-8, BIBX 1382
197359-31-2 202196-59-6, GW5289 202271-41-8, GW0277 202272-68-2,
GW2974 202272-69-3, GW9263 204005-46-9, SU-5416 205923-56-4, C225
212141-54-3, CGP-79787 212142-18-2, PTK 787 220127-57-1, Imatinib
mesylate 231277-92-2, GW572016 257933-82-7, EKB-569 259672-35-0,
BIBX1522 267243-28-7 **289499-45-2**, CI-1033 305820-76-2,
PD-173956 339151-96-1, EMD 82633 339152-71-5, MDX-210 339177-26-3,
ABX-EGF 339186-66-2, EMD-55900 339186-68-4, EMD-72000 339526-85-1,
MDX-260 378223-57-5 386744-54-3, GW 4263 386744-56-5, GW 9525
403850-97-5, ZM-254530 437755-78-7, GW-2016 713078-32-1 713145-03-0,
PD 171026 713145-04-1, PD 090560 713145-05-2, EMD 6200 713145-06-3,
BAB 447 713145-70-1, H 447 713145-71-2, ZD 1838 713145-74-5, CGP
59326B 713145-75-6, CGP 74321 713145-76-7, CGP 76627 713145-77-8,
DWP 408 713145-80-3, S 96-8045 713145-81-4, GEM 220 713145-82-5, AR
639 713145-83-6, DAB 720 713145-86-9, OLX 103 713145-89-2, NX 278L
713145-95-0, PD 169450 713146-03-3, QX 101 713146-04-4, FCE 26806
713146-05-5, CGP 60261 713146-06-6, PD 159973 713146-07-7, GW 282974
713146-08-8, CP 292597 713146-09-9, GW 7072X 713146-10-2, FCE 27119
713146-11-3, PD 154233 713146-12-4, PD 151514 713146-13-5, KW 6151
713146-16-8, C 1033 713146-17-9, GW 211 713146-18-0, GW 5949
713146-20-4, PD 13530 713146-21-5, CGP 5211
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity);
THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as EGFR antagonist; COX-2 inhibitor in combination with epidermal growth factor receptor antagonist for prevention or treatment of neoplasia)

IT 15663-27-1, **Cisplatin**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity);
THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in antitumor combination with S836; COX-2 inhibitor in combination with epidermal growth factor receptor antagonist for prevention or treatment of neoplasia)

IT 713146-27-1, S 836
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity);
THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in antitumor combination with **cisplatin**; COX-2 inhibitor in combination with epidermal growth factor receptor antagonist for prevention or treatment of neoplasia)

IT **289499-45-2**, CI-1033
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity);
THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as EGFR antagonist; COX-2 inhibitor in combination with epidermal growth factor receptor antagonist for prevention or treatment of neoplasia)

L10 ANSWER 4 OF 13 MEDLINE on STN DUPLICATE 1
AB CI-1033 is a quinazoline-based HER family tyrosine kinase inhibitor that is currently being evaluated as a potential anticancer agent. The present study examines the molecular mechanism by which CI-1033 induces apoptosis either as a single agent or in combination with **radiation**. Although CI-1033 alone did not induce apoptosis, the simultaneous exposure of cells to CI-1033 and **radiation** induced significant levels of

apoptosis. The sequential treatment of cells with CI-1033 followed by **radiation** induced an even greater effect with 62.6% of cells undergoing apoptosis but this enhanced effect was not seen if cells were treated first with **radiation** and then CI-1033. The combination treatment induces apoptosis of HuCCT-1 via upregulation of FasL and Bid cleavage. These data suggest that modulation of the Fas-FasL pathway and activation of Bid could be useful for increasing the anti-tumor effect of CI-1033 in this type of cancer.

2004258782. PubMed ID: 15158449. Induction of apoptosis by ionizing **radiation** and CI-1033 in HuCCT-1 cells. Murakami Masateru; Sasaki Tamito; Yamasaki Souichirou; Kuwahara Kenichi; Miyata Hideki; Chayama Kazuaki. (Department of Medicine and Molecular Science, Division of Frontier Medical Science, Programs for Biochemical Research, Graduate School of Biochemical Sciences, Hiroshima University, Hiroshima 734-8551, Japan.. muramura@hiroshima-u.ac.jp) . Biochemical and biophysical research communications, (2004 Jun 18) 319 (1) 114-9. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

TI Induction of apoptosis by ionizing **radiation** and CI-1033 in HuCCT-1 cells.

AB . . . present study examines the molecular mechanism by which CI-1033 induces apoptosis either as a single agent or in combination with **radiation**. Although CI-1033 alone did not induce apoptosis, the simultaneous exposure of cells to CI-1033 and **radiation** induced significant levels of apoptosis. The sequential treatment of cells with CI-1033 followed by **radiation** induced an even greater effect with 62.6% of cells undergoing apoptosis but this enhanced effect was not seen if cells were treated first with **radiation** and then CI-1033. The combination treatment induces apoptosis of HuCCT-1 via upregulation of FasL and Bid cleavage. These data suggest. . .

CT . . .

biosynthesis

Membrane Glycoproteins: ME, metabolism

*Morpholines: PD, pharmacology

*Neoplasms: DT, drug therapy

*Neoplasms: RT, radiotherapy

Phosphorylation

Protein-Tyrosine Kinase: ME, metabolism

Radiation, Ionizing

Receptor, Epidermal Growth Factor: ME, metabolism

RN **289499-45-2 (CI1033)**

L10 ANSWER 5 OF 13 MEDLINE on STN

AB The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein that constitutes one of four members of the erbB family of tyrosine kinase receptors. Binding of EGFR to its cognate ligands leads to autophosphorylation of receptor tyrosine kinase and subsequent activation of signal transduction pathways that are involved in regulating cellular proliferation, differentiation, and survival. Although present in normal cells, EGFR is overexpressed in a variety of tumor cell lines and has been associated with poor prognosis and decreased survival. EGFR activation also plays a role in resistance to chemotherapy and **radiation** treatment in tumor cells. Over the past two decades, much effort has been directed at developing anticancer agents that can interfere with EGFR activity. The most common pharmacologic approaches to inhibiting EGFR have been to develop monoclonal antibodies and small-molecule inhibitors. Monoclonal antibodies block ligand binding to the extracellular domain, whereas the small-molecule inhibitors exert

their effects at the intracellular portion of the receptor to prevent tyrosine kinase phosphorylation and subsequent activation of signal transduction pathways. A number of EGFR inhibitors have been developed that can arrest tumor growth and, in some cases, cause tumor regression. When used in combination with cytotoxic treatments, chemotherapy, and **radiation**, EGFR inhibitors have been able to potentiate their anticancer activity.

2004244349. PubMed ID: 15142631. Review of epidermal growth factor receptor biology. Herbst Roy S. (Department of Thoracic Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030-4009, USA.. rherbst@mdanderson.org) . International journal of radiation oncology, biology, physics, (2004) 59 (2 Suppl) 21-6. Ref: 51. Journal code: 7603616. ISSN: 0360-3016. Pub. country: United States. Language: English.

AB . . . has been associated with poor prognosis and decreased survival. EGFR activation also plays a role in resistance to chemotherapy and **radiation** treatment in tumor cells. Over the past two decades, much effort has been directed at developing anticancer agents that can. . . can arrest tumor growth and, in some cases, cause tumor regression. When used in combination with cytotoxic treatments, chemotherapy, and **radiation**, EGFR inhibitors have been able to potentiate their anticancer activity.

CT . . . Resistance, Neoplasm
Morpholines: TU, therapeutic use
*Neoplasm Proteins: AI, antagonists & inhibitors
*Neoplasm Proteins: PH, physiology
Quinazolines: TU, therapeutic use
Radiation Tolerance
*Receptor, Epidermal Growth Factor: AI, antagonists & inhibitors
*Receptor, Epidermal Growth Factor: PH, physiology
Receptor, erbB-2: ME, metabolism

RN 184475-35-2 (gefitinib); **289499-45-2 (CI1033)**

L10 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

AB The invention relates to a use of (an) EGF receptor antagonist(s)/inhibitor(s) for the preparation of a pharmaceutical composition for the prevention, amelioration or treatment of gastric carcinomas, preferably for the prevention, amelioration or treatment of diffuse gastric carcinomas. Furthermore, the invention provides for a method for treating or for preventing gastric carcinomas, in particular diffuse gastric carcinomas comprising the administration of at least one EGF receptor antagonist/inhibitor to a subject in need of such a treatment or prevention.

2003:931201 Document Number 140:13024 EGF receptor antagonists in the treatment of gastric cancer. Luber, Birgit; Fuchs, Margit Roswitha; Hoefler, Heinz; Fend, Falko; Gamboa-Dominguez, Armando (Technische Universitaet Muenchen, Germany). PCT Int. Appl. WO 2003097086 A2 20031127, 153 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-EP5057 20030514. PRIORITY: US 2002-PV380285

20020515; EP 2003-4524 20030228.
IT 51-21-8, 5-Fu 446-72-0, Genistein 15663-27-1, **Cisplatin** 33419-42-0, **Etoposide** 153436-53-4, Tyrphostin AG1478 171179-06-9, PD 158780 183319-69-9, OSI-774 184475-35-2, ZD-1839 187724-61-4, PKI-166 **289499-45-2**, CI-1033 628738-05-6, CPG 59326
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(EGF receptor antagonists in treatment of gastric cancer)
IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(EGF receptor antagonists in treatment of gastric cancer)

L10 ANSWER 7 OF 13 MEDLINE on STN
AB Progress in identifying and understanding the molecular and cellular causes of cancer has led to the discovery of anomalies that characterize cancer cells and that represent targets for the development of cancer therapeutics. One such target is the epidermal growth factor receptor (EGFR), a transmembrane protein that is frequently dysregulated in cancer cells. Preclinical studies have demonstrated that pharmacologic interventions that abrogate EGFR dysfunction result in antitumor effects. On the basis of these findings, therapeutic strategies to inhibit EGFR and EGFR-related pathways, including the use of monoclonal antibodies against the extracellular ligand-binding domain of EGFR and small-molecule inhibitors of the tyrosine kinase activity of EGFR, have entered clinical testing where they have demonstrated favorable safety profiles and adequate clinical pharmacology. Further development of these agents has been fueled by evidence of their antitumor activities, both as single agents and in combination with chemotherapy and **radiation** therapy. Areas that require investigation are the definition of patient populations most likely to derive benefits from these drugs, the implementation of biologic correlative studies to aid the selection of pharmacodynamically relevant doses and schedules, the characterization of population pharmacokinetic parameters and pharmacogenomic variables, and the most appropriate clinical scenario for proceeding with the clinical development of these agents.
2003285833. PubMed ID: 12813169. Developing inhibitors of the epidermal growth factor receptor for cancer treatment. Grunwald Viktor; Hidalgo Manuel. (The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD 21231-1000, USA.) Journal of the National Cancer Institute, (2003 Jun 18) 95 (12) 851-67. Ref: 184. Journal code: 7503089. ISSN: 1460-2105. Pub. country: United States. Language: English.
AB . . . agents has been fueled by evidence of their antitumor activities, both as single agents and in combination with chemotherapy and **radiation** therapy. Areas that require investigation are the definition of patient populations most likely to derive benefits from these drugs, the. . .
RN 184475-35-2 (gefitinib); **289499-45-2 (CI1033)**

L10 ANSWER 8 OF 13 MEDLINE on STN
AB EGFR (epidermal growth factor receptor) is a transmembrane glycoprotein highly expressed in head and neck squamous cell carcinoma (HNSCC). Once triggered by ligands, tyrosine kinase located at their inner part is phosphorylated, initiating signal transduction pathways towards the nucleus. Two categories of EGFR inhibitors are affordable: the former group includes monoclonal antibodies whereas the latter regards tyrosine

kinase inhibitors (ITK). Acting more as cytostatic than cytotoxic agents, they may potentiate both chemotherapy (CT) and **radiation** therapy (RT). Characterized by a spectrum of toxicity that does not overlap that of CT or RT, they may be associated with these treatments. First clinical trials have demonstrated the feasibility of their administration. Side-effects merely consist of skin reactions and digestive symptoms; their intensity is generally mild and they resolve at the completion of treatment. As of yet, response rates are sometimes astounding but are still disparate. Randomized studies are ongoing. A better definition of EGFR status is warranted. Other data regarding interactions between her-family members, ligands parameters and the cascade regulation of signal transduction would certainly enable to better define the clinical applications of this new therapeutical approach.

2004062562. PubMed ID: 14763143. [Targeting of epidermal growth factor receptor and applications in ORL cancer]. Ciblage du recepteur du facteur de croissance epidermique et applications en cancerologie ORL. Tortochaux Jacques; Aunoble Benedicte; Rolhion Christine; Bourhis Jean. (Departement de radiotherapie, Centre Jean-Perrin, BP 392, 63011 Clermont-Ferrand.. jtortochaux@cjp.u-clermont1.fr) . Bulletin du cancer, (2003 Nov) 90 Spec No S220-7. Ref: 44. Journal code: 0072416. ISSN: 0007-4551. Pub. country: France. Language: French.

AB . . . latter regards tyrosine kinase inhibitors (ITK). Acting more as cytostatic than cytotoxic agents, they may potentiate both chemotherapy (CT) and **radiation** therapy (RT). Characterized by a spectrum of toxicity that does not overlap that of CT or RT, they may be. . .

RN 184475-35-2 (gefitinib); **289499-45-2 (CI1033)**

L10 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

AB The invention relates to methods and products for treating cancer. In particular the invention relates to combinations of nucleic acids and antibodies for the treatment and prevention of cancer. The invention also relates to diagnostic methods for screening cancer cells.

2001:935435 Document Number 136:84677 Methods for enhancing antibody-induced cell lysis and treating cancer. Weiner, George; Hartmann, Gunther (University of Iowa Research Foundation, USA). PCT Int. Appl. WO 2001097843 A2 20011227, 312 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US20154 20010622. PRIORITY: US 2000-PV213346 20000622.

IT 50-07-7, Mitomycin C 50-18-0, Cyclophosphamide 50-76-0, Dactinomycin 50-91-9, Floxuridine 51-21-8, 5-Fluorouracil 52-24-4, Thiotepa 53-19-0, Mitotane 55-86-7, Mechlorethamine hydrochloride 55-98-1, Busulfan 57-22-7, Vincristine 59-05-2, Methotrexate 66-22-8, Uracil, biological studies 69-74-9, Cytarabine hydrochloride 125-84-8, Aminoglutethimide 127-07-1, Hydroxylurea 129-46-4 143-67-9, Vinblastine sulfate 145-63-1, Suramin 148-82-3, Melphalan 154-42-7, Thioguanine 154-93-8, Carmustine 305-03-3, Chlorambucil 320-67-2, Azacitidine 366-70-1, Procarbazine hydrochloride 459-86-9, Mitoguazone 555-57-7, Pargyline 645-05-6, Hexamethylmelamine 1605-68-1D, Taxane, analogs 3094-09-5, Furtulon 3778-73-2, Ifosfamide 4291-63-8, Leustatin 4342-03-4, Dacarbazine 7440-24-6D, Strontium, derivs.

9015-68-3, Asparaginase 11056-06-7, Bleomycin 11096-26-7, Erythropoietin 13010-20-3D, Nitrosourea, derivs. 13010-47-4, Lomustine 13311-84-7, Flutamide 13909-09-6, Semustine 14769-73-4 15663-27-1 17902-23-7, Tegafur 18378-89-7, Plicamycin 18883-66-4, Streptozocin 19767-45-4, Mesnex 23214-92-8 23541-50-6, Daunorubicin hydrochloride 25191-14-4, Poly(G) 25316-40-9, **Adriamycin** 29767-20-2, Vumon 31441-78-8, Mercaptopurine 33069-62-4 33419-42-0 38270-90-5, Metastron 39325-01-4, Picibanil 41575-94-4, Paraplatin 51264-14-3, Amsacrine 52205-73-9, Estramustine phosphate sodium 53910-25-1, Pentostatin 54965-24-1, Tamoxifen citrate 56124-62-0, Valrubicin 59917-39-4, Vindesine sulfate 59989-18-3, Eniluracil 66849-34-1, Dexifosfamide 70476-82-3, Novantrone 74381-53-6, Leuprolide acetate 74578-38-4, UFT 77907-69-8, Interferon alfa-2a 83150-76-9, Octreotide 83869-56-1, GM-CSF 85622-93-1, Temozolomide 90409-78-2, Polifeprosan 91421-43-1, 9-Aminocamptothecin 95058-81-4, **Gemcitabine** 97682-44-5, Camptosar 98530-12-2, Interferon alfa-2b 100286-90-6, Campto 102409-92-7, FK 317 112522-64-2, CI-994 112887-68-0, Raltitrexed 114977-28-5, Taxotere 119413-54-6, Hycamtin 119876-18-5 120685-11-2, PKC412 121584-18-7, Valspodar 122051-95-0 122111-03-9, Gemzar 123948-87-8, **Topotecan** 129298-91-5, TNP-470 129580-63-8, BMS 182751 130370-60-4, Batimastat 141907-41-7, Matrix metalloproteinase 145918-75-8, BCH-4556 146426-40-6, HMR 1275 150399-23-8, LY231514 151823-14-2, CS-682 153537-73-6, ZD 9331 154039-60-8 154361-50-9, **Capecitabine** 159776-69-9, LU 103793 159997-94-1 162706-37-8, LU 79553 165668-41-7, E7070 169799-04-6 169869-90-3, DX8951f 174722-31-7, Rituximab 179545-77-8, BAY 12-9566 181630-15-9, ZD 0473 183012-14-8, YM 116 183319-69-9, CP 358774 184046-91-1 190454-58-1, VX-853 192329-42-3, AG3340 209164-46-5, CDP 845 209973-83-1, BLP 25 213327-37-8, OvaRex 259188-38-0, D 2163 **289499-45-2**, PD 183805 340014-19-9, Melacine 386211-12-7, AG 3433 386211-13-8, ZD 0101 386211-20-7, ISI 641 386211-21-8, ODN 698 386211-47-8, Lemonal DP 2202 386211-48-9, CP 609754
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunostimulatory nucleic acids and antibody specific to CD20, CD22, CD19 or CD40 for inducing cell lysis and treating cancer)

IT **289499-45-2**, PD 183805
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunostimulatory nucleic acids and antibody specific to CD20, CD22, CD19 or CD40 for inducing cell lysis and treating cancer)

L10 ANSWER 10 OF 13 MEDLINE on STN

AB The ErbB receptor family is implicated in the malignant transformation of several tumor types and is overexpressed frequently in breast, ovarian, and other tumors. The mechanism by which CI-1033 and **gemcitabine**, either singly or in combination, kill tumor cells was examined in two breast lines, MDA-MB-453 and BT474; both overexpress the ErbB-2 receptor. CI-1033, a potent inhibitor of the ErbB family of receptor tyrosine kinases, reduced levels of activated Akt in MDA-MB-453 cells. This effect alone, however, did not induce apoptosis in these cells. **Gemcitabine** treatment resulted in a moderate increase in the percentage of apoptotic cells that was accompanied by activation of p38 and MAPK (ERK1/2). CI-1033 given 24 h after **gemcitabine** produced a significant increase in the apoptotic fraction ov
with either drug alone. During the combined treatment
activated, whereas Akt and activated MAPK were suppresse
of CI-1033 with the phosphatidylinositol 3-kinase inhibi
the MAPK/ERK kinase inhibitor PD 098059 in combination w

gemcitabine produced the same results as the combination of CI-1033 and **gemcitabine**. p38 suppression by SB203580 prevented the enhanced cell kill by CI-1033. In contrast to MDA-MB-453, BT474 cells exhibited activated p38 under unstressed conditions as well as activated Akt and MAPK. Treatment of BT474 cells with CI-1033 inhibited both the phosphorylation of Akt and MAPK and resulted in a 47% apoptotic fraction. **Gemcitabine** did not cause apoptosis in the BT474 cells. These data indicate that suppression of Akt and MAPK in the presence of activated p38 results in cell death and a possible mechanism for the enhanced apoptosis produced by the combination of CI-1033 and **gemcitabine** in MDA-MB-453 cells. Furthermore, tumors that depend on ErbB receptor signaling for survival and exhibit activated p38 in the basal state may be susceptible to apoptosis by CI-1033 as a single agent.

2001370796. PubMed ID: 11278435. Akt, MAPK (Erk1/2), and p38 act in concert to promote apoptosis in response to ErbB receptor family inhibition. Nelson J M; Fry D W. (Pfizer Global Research and Development, Ann Arbor, Michigan 48105, USA.. James.Nelson@Pfizer.com) . Journal of biological chemistry, (2001 May 4) 276 (18) 14842-7. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB . . . of several tumor types and is overexpressed frequently in breast, ovarian, and other tumors. The mechanism by which CI-1033 and **gemcitabine**, either singly or in combination, kill tumor cells was examined in two breast lines, MDA-MB-453 and BT474; both overexpress the. . . kinases, reduced levels of activated Akt in MDA-MB-453 cells. This effect alone, however, did not induce apoptosis in these cells. **Gemcitabine** treatment resulted in a moderate increase in the percentage of apoptotic cells that was accompanied by activation of p38 and MAPK (ERK1/2). CI-1033 given 24 h after **gemcitabine** produced a significant increase in the apoptotic fraction over treatment with either drug alone. During the combined treatment p38 remained. . . suppressed. Substitution of CI-1033 with the phosphatidylinositol 3-kinase inhibitor LY294002 and the MAPK/ERK kinase inhibitor PD 098059 in combination with **gemcitabine** produced the same results as the combination of CI-1033 and **gemcitabine**. p38 suppression by SB203580 prevented the enhanced cell kill by CI-1033. In contrast to MDA-MB-453, BT474 cells exhibited activated p38. . . of BT474 cells with CI-1033 inhibited both the phosphorylation of Akt and MAPK and resulted in a 47% apoptotic fraction. **Gemcitabine** did not cause apoptosis in the BT474 cells. These data indicate that suppression of Akt and MAPK in the presence. . . p38 results in cell death and a possible mechanism for the enhanced apoptosis produced by the combination of CI-1033 and **gemcitabine** in MDA-MB-453 cells. Furthermore, tumors that depend on ErbB receptor signaling for survival and exhibit activated p38 in the basal. . .

RN **103882-84-4 (gemcitabine)**; 154447-36-6 (2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one); **289499-45-2 (CI1033)**; 951-77-9 (Deoxycytidine)

L10 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

AB In the setting of target-based anticancer drug development, it is critical to establish that the observed preclin. activity can be attributed to modulation of the intended target in early phase trials in human subjects. This paradigm of target modulation allows the authors to determine a Phase II or III dose (optimal biochem./biol. modulatory dose) that may not necessarily be the maximum tolerated dose. A major obstacle to target-based (often cytostatic) drug development has been obtaining relevant tumor tissue during clin. trials of these novel agents for laboratory anal. of the putative

marker of drug effect. From 1989 to present, the authors have completed seven clin. trials in which the end point was a biochem. or biol. modulatory dose in human tumor tissues (not surrogate tissue). Eligibility enrollment required that patients have a biopsiable lesion either with computerized tomog. (CT) guidance or direct visualization and consent to sequential (pre and posttreatment) biopsies. A total of 192 biopsies were performed in 107 patients. All but 8 patients had sequential pre and posttreatment biopsies. Seventy-eight (73%) of the 107 patients had liver lesion biopsies. In eight patients, either one or both biopsies contained insufficient viable tumor tissue or no tumor tissue at all for anal. Of a total of 99 patients in whom the authors attempted to obtain paired biopsies, a total of 87 (88%) were successful. Reasons for failure included patient refusal for a second biopsy (n = 2), vasovagal reaction with first biopsy precluding a second biopsy (n = 1), subcapsular hepatic bleeding (n = 1), and most commonly obtaining necrotic tumor, fibrous, or normal tissue in one of the two sequential biopsies (n = 8). This is the first and largest reported series demonstrating that with adequate precautions and experience, sequential tumor biopsies are feasible and safe during early phase clin. trials.

2001:799778 Document Number 136:112324 Sequential tumor biopsies in early phase clinical trials of anticancer agents for pharmacodynamic evaluation. Dowlati, Afshin; Haaga, John; Remick, Scot C.; Spiro, Timothy P.; Gerson, Stanton L.; Liu, Lili; Berger, Sosamma J.; Berger, Nathan A.; Willson, James K. V. (Division of Hematology/Oncology, Department of Medicine and Developmental Therapeutics Program, Ireland Cancer Center at University Hospitals of Cleveland and Case Western Reserve University, Cleveland, OH, 44106, USA). Clinical Cancer Research, 7(10), 2971-2976 (English) 2001. CODEN: CCREF4. ISSN: 1078-0432. Publisher: American Association for Cancer Research.

IT 154-93-8, BCNU 15663-27-1, **Cisplatin** 18883-66-4, Streptozotocin 19916-73-5, O6-Benzylguanine 23214-92-8, Doxorubicin 33069-62-4, **Paclitaxel** 60084-10-8, Tiazofurin 65646-68-6, Fenretinide 85622-93-1, Temozolomide 97682-44-5, Irinotecan 123948-87-8, **Topotecan** 204005-46-9, SU5416 **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sequential human tumor biopsies in early phase clin. trials of anticancer agents for pharmacodynamic evaluation)

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sequential human tumor biopsies in early phase clin. trials of anticancer agents for pharmacodynamic evaluation)

L10 ANSWER 12 OF 13 MEDLINE on STN DUPLICATE 2

AB Because the activities of HER family members are elevated and/or aberrant in a variety of human neoplasms, these cell surface receptors are receiving increasing attention as potential therapeutic targets. In the present study, we examined the effect of combining the HER family tyrosine kinase inhibitor CI1033 (PD 183805) with the topoisomerase (topo) I poison 7-ethyl-10-hydroxycamptothecin (SN-38), the active metabolite of irinotecan, in a number of different cell lines. Colony-forming assays revealed that the antiproliferative effects of simultaneous treatment with CI1033 and SN-38 were synergistic in T98G glioblastoma cells and HCT8 colorectal carcinoma cells, whereas sequential treatments were additive at best. In additional studies examining the mechanistic basis for these

findings in T98G cells, immunoblotting revealed that the inhibitory effects of CI1033 on epidermal growth factor receptor autophosphorylation were unaffected by SN-38. Likewise, CI1033 had no effect on topo I polypeptide levels, localization, or activity. Nonetheless, CI1033 markedly enhanced the number of covalent topo I-DNA complexes stabilized by SN-38 or the related agent **topotecan** (TPT). Analysis of intracellular SN-38 levels by high-performance liquid chromatography and intracellular TPT levels by flow microfluorometry revealed that CI1033 increased the steady-state accumulation of SN-38 and TPT by 9.4 +/- 1.9- and 1.8 +/- 0.2-fold, respectively. Further evaluation revealed that the initial rate of TPT uptake was unaffected by CI1033, whereas the rate of efflux was markedly diminished. Additional studies demonstrated that T98G and HCT8 cells express the breast cancer resistance protein (BCRP), a recently cloned ATP binding cassette transporter. Moreover, CI1033 enhanced the uptake and cytotoxicity of SN-38 and TPT in cells transfected with BCRP but not empty vector. Conversely, CI1033 accumulation was diminished in cells expressing BCRP, suggesting that CI1033 is a substrate for this efflux pump. These results indicate that CI1033 can modulate the accumulation and subsequent cytotoxicity of two widely used topo I poisons in cells that have no history of previous exposure to these agents.

2001126937. PubMed ID: 11212277. The HER tyrosine kinase inhibitor CI1033 enhances cytotoxicity of 7-ethyl-10-hydroxycamptothecin and **topotecan** by inhibiting breast cancer resistance protein-mediated drug efflux. Erlichman C; Boerner S A; Hallgren C G; Spieker R; Wang X Y; James C D; Scheffer G L; Maliepaard M; Ross D D; Bible K C; Kaufmann S H. (Division of Medical Oncology, Mayo Clinic, Rochester, Minnesota 55905, USA.) Cancer research, (2001 Jan 15) 61 (2) 739-48. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

TI The HER tyrosine kinase inhibitor CI1033 enhances cytotoxicity of 7-ethyl-10-hydroxycamptothecin and **topotecan** by inhibiting breast cancer resistance protein-mediated drug efflux.

AB . . . or activity. Nonetheless, CI1033 markedly enhanced the number of covalent topo I-DNA complexes stabilized by SN-38 or the related agent **topotecan** (TPT). Analysis of intracellular SN-38 levels by high-performance liquid chromatography and intracellular TPT levels by flow microfluorometry revealed that CI1033. . .

CT . . .
& inhibitors
Receptor, Epidermal Growth Factor: DE, drug effects
Receptor, Epidermal Growth Factor: ME, metabolism
Recombinant Fusion Proteins: GE, genetics
Topotecan: ME, metabolism
***Topotecan: PD, pharmacology**
Transfection
Tumor Cells, Cultured
Tumor Stem Cell Assay
Tumor Stem Cells: DE, drug effects

RN **123948-87-8 (Topotecan); 289499-45-2 (CI1033);** 7689-03-4 (Camptothecin); 86639-52-3 (7-ethyl-10-hydroxycamptothecin)

L10 ANSWER 13 OF 13 MEDLINE on STN DUPLICATE 3

AB Irreversible inhibitors of the epidermal growth factor receptor (EGFR) are showing promise in clinical trials. This report is the first to show that inhibition of the EGFR tyrosine kinase by an irreversible binder synergizes with **cisplatin**, at least in EGFR-overexpressing tissue culture cell lines in vitro. Unlike previous synergies demonstrated between ErbB2 blockade and DNA-damaging drugs, the synergy

between the irreversible EGFR inhibitor and **cisplatin** does not appear to involve the repair of DNA-**cisplatin** adducts. Given the current clinical data, this combination may be of more than theoretical interest.

2001557696. PubMed ID: 11604556. Evidence for epidermal growth factor receptor-enhanced chemosensitivity in combinations of **cisplatin** and the new irreversible tyrosine kinase inhibitor CI-1033. Gieseg M A; de Bock C; Ferguson L R; Denny W A. (Auckland Cancer Society Research Centre, Faculty of Medical & Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1000, New Zealand.. Michael.Gieseg@pfizer.com) . Anti-cancer drugs, (2001 Sep) 12 (8) 683-90. Journal code: 9100823. ISSN: 0959-4973. Pub. country: England: United Kingdom. Language: English.

TI Evidence for epidermal growth factor receptor-enhanced chemosensitivity in combinations of **cisplatin** and the new irreversible tyrosine kinase inhibitor CI-1033.

AB . . . This report is the first to show that inhibition of the EGFR tyrosine kinase by an irreversible binder synergizes with **cisplatin**, at least in EGFR-overexpressing tissue culture cell lines in vitro. Unlike previous synergies demonstrated between ErbB2 blockade and DNA-damaging drugs, the synergy between the irreversible EGFR inhibitor and **cisplatin** does not appear to involve the repair of DNA-**cisplatin** adducts. Given the current clinical data, this combination may be of more than theoretical interest.

CT . . .

Cell: EN, enzymology
Carcinoma, Squamous Cell: GE, genetics
Carcinoma, Squamous Cell: PA, pathology
Cell Division: DE, drug effects
Cells, Cultured
***Cisplatin: AD, administration & dosage**
*DNA Adducts: DE, drug effects
DNA Repair: DE, drug effects
Drug Administration Schedule
Drug Synergism
Enzyme. . .

RN **15663-27-1 (Cisplatin); 289499-45-2 (CI1033)**

CN 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (DNA Adducts); 0 (Enzyme Inhibitors); 0 (Morpholines); 0 (**cisplatin**-DNA adduct); EC 1.13.12.- (Luciferase); EC 2.7.1.112 (Receptor, Epidermal Growth Factor)

10/592,291

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=> d l1 1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   289499-45-2  REGISTRY
CN   2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-
     morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI)  (CA INDEX
     NAME)
OTHER NAMES:
CN   Canertinib dihydrochloride
CN   CI 1033
CN   PD 183805
DR   338796-35-3
MF   C24 H25 Cl F N5 O3 . 2 Cl H
SR   CAS Client Services
LC   STN Files:   ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CAPLUS, EMBASE,
       IMSRESEARCH, IPA, MEDLINE, PHAR, PROUSDDR, SYNTHLINE, TOXCENTER, USAN,
       USPATFULL
DT.CA  CAplus document type:  Conference; Journal; Patent
RL.P   Roles from patents:  BIOL (Biological study); PREP (Preparation); PRP
       (Properties); USES (Uses)
RLD.P  Roles for non-specific derivatives from patents:  BIOL (Biological
       study); USES (Uses)
RL.NP  Roles from non-patents:  ANST (Analytical study); BIOL (Biological
       study); PROC (Process); USES (Uses)
CRN  (267243-28-7)
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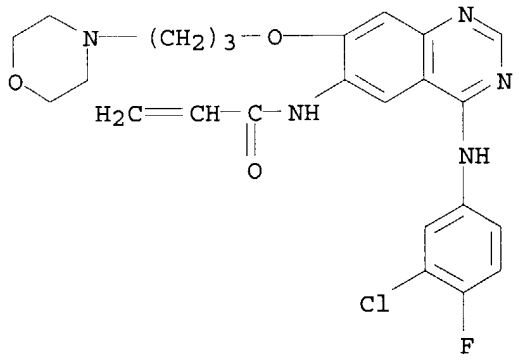

●2 HCl

37 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
37 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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10/632,281

=> d his

(FILE 'HOME' ENTERED AT 22:01:34 ON 17 SEP 2004)

FILE 'REGISTRY' ENTERED AT 22:01:44 ON 17 SEP 2004
E CI-1033/CN
E CI 1033/CN
L1 1 S E3

FILE 'MEDLINE, HCAPLUS' ENTERED AT 22:03:15 ON 17 SEP 2004
L2 10 S L1 AND ERBB(P)TYROSIN?(P)KINAS?
L3 8 DUP REM L2 (2 DUPLICATES REMOVED)

FILE 'STNGUIDE' ENTERED AT 22:04:25 ON 17 SEP 2004

FILE 'MEDLINE, HCAPLUS' ENTERED AT 22:05:56 ON 17 SEP 2004
L4 1839 S ERBB(P)TYROSIN?(P)KINAS?
L5 1278 S L4 AND (CANCER? OR CARCINOM? OR GLIOM? OR TUMOR? OR TUMOUR? O
L6 60 S L5 AND (GEMCITABIN? OR PACLITAX? OR DOCETAX? OR CISPLATIN? O
L7 41 DUP REM L6 (19 DUPLICATES REMOVED)

FILE 'STNGUIDE' ENTERED AT 22:11:21 ON 17 SEP 2004

FILE 'MEDLINE, HCAPLUS' ENTERED AT 22:13:08 ON 17 SEP 2004
L8 27 S L7 AND PY<=2002

FILE 'STNGUIDE' ENTERED AT 22:14:02 ON 17 SEP 2004

FILE 'MEDLINE, HCAPLUS' ENTERED AT 22:17:20 ON 17 SEP 2004
L9 16 S L1 AND (GEMCITABIN? OR PACLITAX? OR DOCETAX? OR CISPLATIN? OR
L10 13 DUP REM L9 (3 DUPLICATES REMOVED)

FILE 'STNGUIDE' ENTERED AT 22:18:22 ON 17 SEP 2004

FILE 'MEDLINE' ENTERED AT 22:13:08 ON 17 SEP 2004

FILE 'HCAPLUS' ENTERED AT 22:13:08 ON 17 SEP 2004

=> s l7 and py<=2002
L8 27 L7 AND PY<=2002

=> d l8 abs ibib kwic hitrn 1-27

L8 ANSWER 1 OF 27 MEDLINE on STN

AB The introduction of biologically active agents that interfere with the epidermal growth factor receptor (EGFR) provides a promising opportunity to improve **cancer** treatment outcomes. Several EGFR-selective agents, such as humanized monoclonal antibodies and small molecule, orally available **tyrosine kinase** inhibitors have shown antitumor activity in early clinical trials in advanced **cancer** patients. Preclinical studies have demonstrated enhanced **radiation**- and chemotherapy-induced **tumor** cytotoxicity when EGFR antagonists are implemented. More broadly, recent clinical trials have confirmed improved survival with combinations of HER-2 (a member of the **ErbB** family of receptors) targeted antibodies and chemotherapy in patients with advanced breast **cancer**. A landmark trial combining C225 antiEGFR antibody with **radiation** therapy for patients with locally advanced head and neck **cancer** has just completed accrual. Thus, emerging rapidly are **cancer** treatment strategies based on an improved understanding of the specific cellular and molecular abnormalities of individual **tumors**.

ACCESSION NUMBER: 2003133450 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12647989
TITLE: Interference with EGFR signaling: paradigm for improving **radiation** response in **cancer** treatment.
AUTHOR: Raben David; Bianco Cataldo; Helfrich Barb; Weng Elaine; Ciardiello Fortunato; Harari Paul
CORPORATE SOURCE: University of Colorado Health Sciences Center, Anschutz Cancer Pavilion, Department of Radiation Oncology, Aurora 80010-0510, USA.. david.raben@uchsc.edu
SOURCE: Expert review of anticancer therapy, **(2002 Aug)** 2 (4) 461-71. Ref: 64
Journal code: 101123358. ISSN: 1473-7140.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030322
Last Updated on STN: 20030430
Entered Medline: 20030429

TI Interference with EGFR signaling: paradigm for improving **radiation** response in **cancer** treatment.

SO Expert review of anticancer therapy, **(2002 Aug)** 2 (4) 461-71. Ref: 64

Journal code: 101123358. ISSN: 1473-7140.
AB . . . introduction of biologically active agents that interfere with the epidermal growth factor receptor (EGFR) provides a promising opportunity to improve **cancer** treatment outcomes. Several EGFR-selective agents, such as humanized monoclonal antibodies and small molecule, orally available **tyrosine kinase** inhibitors have shown antitumor activity in early clinical trials in advanced **cancer** patients. Preclinical studies have demonstrated enhanced **radiation**- and chemotherapy-induced **tumor** cytotoxicity when EGFR antagonists are implemented. More broadly, recent clinical trials have confirmed improved survival with combinations of HER-2 (a member of the **ErbB** family of receptors) targeted antibodies and chemotherapy in patients with advanced breast **cancer**. A landmark trial combining C225 antiEGFR antibody with **radiation** therapy for patients with locally advanced head and neck **cancer** has just completed accrual. Thus, emerging rapidly are **cancer** treatment strategies based on an improved understanding of the specific cellular and molecular abnormalities of individual **tumors**.
CT . . .
Monoclonal: PD, pharmacology
Antibodies, Monoclonal: TU, therapeutic use
Clinical Trials, Phase III
Enzyme Inhibitors: PD, pharmacology
Genes, erbB-1: GE, genetics
***Neoplasms: RT, radiotherapy**
Protein-Tyrosine Kinase: AI, antagonists & inhibitors
Quinazolines: TU, therapeutic use
*Receptor, Epidermal Growth Factor: DE, drug effects
*Signal. . .

L8 ANSWER 2 OF 27 MEDLINE on STN
AB HER-2 is a member of the c-**erbB** family of receptor **tyrosine kinases** and is overexpressed by 20-30% of human breast **cancers**. HER-2 overexpression is an independent adverse prognostic factor and may also predict for response to both chemotherapy and endocrine agents. Trastuzumab is a humanised monoclonal antibody that binds with high affinity to the extracellular domain of HER-2. In HER-2-overexpressing preclinical models trastuzumab has been shown to have a marked antiproliferative effect and demonstrates synergy with a number of cytotoxic drugs. Several phase II and phase III clinical trials have now been performed in patients with advanced breast **cancer** that overexpress HER-2. Trastuzumab was initially shown to be active and well tolerated as a single agent in heavily pretreated women. Subsequently, studies of first-line treatment for metastatic breast **cancer** have demonstrated an improvement in survival for trastuzumab when used in combination with either **paclitaxel** or an anthracycline-cyclophosphamide regimen compared with chemotherapy alone. Unexpectedly, the combination of trastuzumab and the anthracycline-containing regimen was associated with a significant incidence of cardiac dysfunction. The benefit of trastuzumab is generally confined to patients whose **tumours** have gene amplification as detected by fluorescence in situ hybridisation (FISH) and this is tightly associated with immunohistochemical (IHC) staining at the highest (3+) level. A small number of patients have IHC 2+ **tumours** together with FISH evidence of gene amplification and may also derive benefit from treatment. Trastuzumab has also been shown to be effective when used as first-line monotherapy for advanced breast **cancer**. Trials to date have

employed trastuzumab in a weekly schedule, but there is emerging evidence that a three-weekly regimen may be as effective. Trastuzumab has shown encouraging activity when used with other agents including **docetaxel** and vinorelbine. The combination of trastuzumab, **docetaxel**, and platinum salts also appears to be very active. The role of trastuzumab as adjuvant therapy for early breast **cancer** is being tested in a number of large randomised trials.

ACCESSION NUMBER: 2002376184 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12121832
TITLE: The development and clinical use of trastuzumab (Herceptin).
AUTHOR: Harries M; Smith I
CORPORATE SOURCE: Breast Unit, The Royal Marsden Hospital and Institute of Cancer Research, Fulham Rd, London SW3 6JJ, UK.. mark.harries@rmh.nthames.nhs.uk
SOURCE: Endocrine-related cancer, **(2002 Jun)** 9 (2) 75-85. Ref: 60
Journal code: 9436481. ISSN: 1351-0088.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020718
Last Updated on STN: 20020906
Entered Medline: 20020904

SO Endocrine-related cancer, **(2002 Jun)** 9 (2) 75-85. Ref: 60
Journal code: 9436481. ISSN: 1351-0088.

AB HER-2 is a member of the c-**erbB** family of receptor **tyrosine kinases** and is overexpressed by 20-30% of human breast **cancers**. HER-2 overexpression is an independent adverse prognostic factor and may also predict for response to both chemotherapy and endocrine agents.. . . of cytotoxic drugs. Several phase II and phase III clinical trials have now been performed in patients with advanced breast **cancer** that overexpress HER-2. Trastuzumab was initially shown to be active and well tolerated as a single agent in heavily pretreated women. Subsequently, studies of first-line treatment for metastatic breast **cancer** have demonstrated an improvement in survival for trastuzumab when used in combination with either **paclitaxel** or an anthracycline-cyclophosphamide regimen compared with chemotherapy alone. Unexpectedly, the combination of trastuzumab and the anthracycline-containing regimen was associated with a significant incidence of cardiac dysfunction. The benefit of trastuzumab is generally confined to patients whose **tumours** have gene amplification as detected by fluorescence in situ hybridisation (FISH) and this is tightly associated with immunohistochemical (IHC) staining at the highest (3+) level. A small number of patients have IHC 2+ **tumours** together with FISH evidence of gene amplification and may also derive benefit from treatment. Trastuzumab has also been shown to be effective when used as first-line monotherapy for advanced breast **cancer**. Trials to date have employed trastuzumab in a weekly schedule, but there is emerging evidence that a three-weekly regimen may be as effective. Trastuzumab has shown encouraging activity when used with other agents including **docetaxel** and vinorelbine. The combination of trastuzumab, **docetaxel**, and platinum salts also appears to be very active. The

role of trastuzumab as adjuvant therapy for early breast **cancer** is being tested in a number of large randomised trials.

CT Check Tags: Female; Human
*Antibodies, Monoclonal: TU, therapeutic use
*Antineoplastic Agents: TU, therapeutic use
***Breast Neoplasms: DT, drug therapy**
Breast Neoplasms: ME, metabolism
Clinical Trials
Receptor, erbB-2: ME, metabolism

L8 ANSWER 3 OF 27 MEDLINE on STN

AB The **erbB** family of receptors, which includes the epidermal growth factor receptor, has been widely implicated in promoting proliferation of malignant cells. The critical role played by epidermal growth factor receptor in **cancer** has resulted in extensive research for selective inhibitors of the epidermal growth factor receptor signalling pathway. Selective small molecule epidermal growth factor receptor-**tyrosine kinase** inhibitors, such as ZD1839 (Iressa), block signal transduction pathways implicated in proliferation and survival of **cancer** cells and other host-dependent processes promoting **cancer** cell growth. In preclinical studies, ZD1839, alone and in combination with other agents, has demonstrated antitumour activity in a range of **tumour** types. Results from Phase I trials, in healthy volunteers and in patients with advanced disease, have shown that ZD1839 has excellent bioavailability and an acceptable tolerability profile. In these studies, ZD1839 has also shown promising clinical activity in patients with a variety of **tumour** types. Furthermore, Phase II studies confirmed clinically meaningful antitumour activity and have demonstrated symptom relief in the second- and third-line treatment of non-small cell lung **cancer**. Phase III trials are currently evaluating ZD1839 in combination with **gemcitabine/cisplatin** or **paclitaxel/carboplatin** as first-line treatment of non-small cell lung **cancer** and an ongoing clinical trial programme is investigating other **tumours** (i.e., head and neck, prostate, colon and breast) and other combinations. This article provides an overview of the current profile of ZD1839.

ACCESSION NUMBER:	2002296525 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 12036427
TITLE:	ZD1839: targeting the epidermal growth factor receptor in **cancer** therapy.
AUTHOR:	Herbst Roy S
CORPORATE SOURCE:	Thoracic/Head and Neck Medical Oncology, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Box 432, Houston, TX 77030, USA.. rherbst@mail.mdanderson.org
SOURCE:	Expert opinion on investigational drugs, **(2002 Jun)** 11 (6) 837-49. Ref: 58 Journal code: 9434197. ISSN: 1354-3784.
PUB. COUNTRY:	England: United Kingdom
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE) General Review; (REVIEW) (REVIEW, TUTORIAL)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	200211
ENTRY DATE:	Entered STN: 20020531 Last Updated on STN: 20021211

Entered Medline: 20021120

TI ZD1839: targeting the epidermal growth factor receptor in **cancer** therapy.

SO Expert opinion on investigational drugs, **(2002 Jun)** 11 (6) 837-49. Ref: 58
Journal code: 9434197. ISSN: 1354-3784.

AB The **erbB** family of receptors, which includes the epidermal growth factor receptor, has been widely implicated in promoting proliferation of malignant cells. The critical role played by epidermal growth factor receptor in **cancer** has resulted in extensive research for selective inhibitors of the epidermal growth factor receptor signalling pathway. Selective small molecule epidermal growth factor receptor-**tyrosine kinase** inhibitors, such as ZD1839 (Iressa), block signal transduction pathways implicated in proliferation and survival of **cancer** cells and other host-dependent processes promoting **cancer** cell growth. In preclinical studies, ZD1839, alone and in combination with other agents, has demonstrated antitumour activity in a range of **tumour** types. Results from Phase I trials, in healthy volunteers and in patients with advanced disease, have shown that ZD1839 has. . . an acceptable tolerability profile. In these studies, ZD1839 has also shown promising clinical activity in patients with a variety of **tumour** types. Furthermore, Phase II studies confirmed clinically meaningful antitumour activity and have demonstrated symptom relief in the second- and third-line treatment of non-small cell lung **cancer**. Phase III trials are currently evaluating ZD1839 in combination with **gemcitabine/cisplatin** or **paclitaxel/carboplatin** as first-line treatment of non-small cell lung **cancer** and an ongoing clinical trial programme is investigating other **tumours** (i.e., head and neck, prostate, colon and breast) and other combinations. This article provides an overview of the current profile. . .

CT . . .

therapeutic use

Clinical Trials
Clinical Trials, Phase I
Clinical Trials, Phase II
Clinical Trials, Phase III
Device Approval
Middle Aged
***Neoplasms: DT, drug therapy**
Neoplasms: EN, enzymology
Quinazolines: PK, pharmacokinetics
Quinazolines: PD, pharmacology
*Quinazolines: TU, therapeutic use
*Receptor, Epidermal Growth Factor: AI, antagonists &. . .

L8 ANSWER 4 OF 27 MEDLINE on STN

AB **ErbB**-2, a member of the epidermal growth factor(EGF) receptor **tyrosine kinase** family, is often overexpressed and/or amplified in breast, ovarian and gastric **cancers**, and other malignancies. **ErbB**-2 is a candidate as one of the best target molecules for **cancer** therapy. Many anti-**ErbB**-2 monoclonal antibodies(MoAbs) have been developed. An inhibitory humanized MoAb shows clinical responses in some breast **cancer** patients, both with MoAb alone and in combination with **Cisplatinum** or other anti-**cancer** drugs. A mouse-human chimeric anti-**ErbB**-2 MoAb CH401 was established and characterized in our

laboratory. CH401 is able to kill **cancer** cells overexpressing **ErbB**-2 both in vitro and in vivo. The analysis of this **tumor** growth inhibition by CH401 made it clear that the cytotoxicity was induced by apoptosis. These results may suggest that CH401 has a therapeutic potential for **ErbB**-2 overexpressing **cancers**. This approach may be particularly valuable as a new type of **cancer** therapy.

ACCESSION NUMBER: 2002174009 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11904957
TITLE: Monoclonal antibody induces apoptosis against **cancer** cells.
AUTHOR: Sasaki Shigeru; Imai Kohzoh
CORPORATE SOURCE: First Department of Internal Medicine, Sapporo Medical University.
SOURCE: Nippon rinsho. Japanese journal of clinical medicine, **(2002 Mar)** 60 (3) 451-6. Ref: 12
Journal code: 0420546. ISSN: 0047-1852.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020322
Last Updated on STN: 20020410
Entered Medline: 20020409

TI Monoclonal antibody induces apoptosis against **cancer** cells.
SO Nippon rinsho. Japanese journal of clinical medicine, **(2002 Mar)** 60 (3) 451-6. Ref: 12
Journal code: 0420546. ISSN: 0047-1852.
AB **ErbB**-2, a member of the epidermal growth factor(EGF) receptor **tyrosine kinase** family, is often overexpressed and/or amplified in breast, ovarian and gastric **cancers**, and other malignancies. **ErbB**-2 is a candidate as one of the best target molecules for **cancer** therapy. Many anti-**ErbB**-2 monoclonal antibodies(MoAbs) have been developed. An inhibitory humanized MoAb shows clinical responses in some breast **cancer** patients, both with MoAb alone and in combination with **Cisplatinum** or other anti-**cancer** drugs. A mouse-human chimeric anti-**ErbB**-2 MoAb CH401 was established and characterized in our laboratory. CH401 is able to kill **cancer** cells overexpressing **ErbB**-2 both in vitro and in vivo. The analysis of this **tumor** growth inhibition by CH401 made it clear that the cytotoxicity was induced by apoptosis. These results may suggest that CH401 has a therapeutic potential for **ErbB**-2 overexpressing **cancers**. This approach may be particularly valuable as a new type of **cancer** therapy.
CT . . .
TU, therapeutic use
*Apoptosis
Apoptosis: DE, drug effects
Chimeric Proteins: PD, pharmacology
Chimeric Proteins: TU, therapeutic use
English Abstract
Mice
***Neoplasms: PA, pathology**

Neoplasms: TH, therapy
*Receptor, erbB-2: IM, immunology
Tumor Cells, Cultured

L8 ANSWER 5 OF 27 MEDLINE on STN
AB The ErbB2 gene encodes a transmembrane growth factor receptor that belongs to the **ErbB** receptor **tyrosine kinase** subfamily. ErbB2 protein is overexpressed in approximately 30% of breast **cancers**. Although controversies exist, data from our laboratory and from clinical trials of trastuzumab indicate that ErbB2 overexpression confers chemoresistance to certain chemotherapeutic agents such as **paclitaxel**. One of the molecular mechanisms of ErbB2-mediated **paclitaxel** resistance is that overexpression of the ErbB2 receptor leads to deregulation of the G2/M cell cycle check-point that inhibits **paclitaxel**-induced apoptosis. Several promising ErbB2-targeting strategies have now been developed to conquer the adverse consequences of ErbB2 overexpression such as **paclitaxel** resistance. Among these, trastuzumab has brought great promise. We have recently shown that trastuzumab can effectively sensitize ErbB2-overexpressing breast **cancer** cells to **paclitaxel** by reversing the antiapoptotic function of ErbB2. Our studies provide additional support for chemotherapy combined with trastuzumab for ErbB2-overexpressing breast **cancers**, and it may bring insights into designing more effective and specific therapies that could offer great benefits to patients.
ACCESSION NUMBER: 2001653479 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11706391
TITLE: Mechanisms of ErbB2-mediated **paclitaxel** resistance and trastuzumab-mediated **paclitaxel** sensitization in ErbB2-overexpressing breast **cancers**.
AUTHOR: Yu D
CORPORATE SOURCE: Department of Molecular and Cellular Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA.
CONTRACT NUMBER: CA60488 (NCI)
SOURCE: Seminars in oncology, **(2001 Oct)** 28 (5 Suppl 16) 12-7. Ref: 41
Journal code: 0420432. ISSN: 0093-7754.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011114
Last Updated on STN: 20020124
Entered Medline: 20011228
TI Mechanisms of ErbB2-mediated **paclitaxel** resistance and trastuzumab-mediated **paclitaxel** sensitization in ErbB2-overexpressing breast **cancers**.
SO Seminars in oncology, **(2001 Oct)** 28 (5 Suppl 16) 12-7. Ref: 41
Journal code: 0420432. ISSN: 0093-7754.
AB The ErbB2 gene encodes a transmembrane growth factor receptor that belongs to the **ErbB** receptor **tyrosine kinase** subfamily. ErbB2 protein is overexpressed in approximately 30% of breast

cancers. Although controversies exist, data from our laboratory and from clinical trials of trastuzumab indicate that ErbB2 overexpression confers chemoresistance to certain chemotherapeutic agents such as **paclitaxel**. One of the molecular mechanisms of ErbB2-mediated **paclitaxel** resistance is that overexpression of the ErbB2 receptor leads to deregulation of the G2/M cell cycle check-point that inhibits **paclitaxel**-induced apoptosis. Several promising ErbB2-targeting strategies have now been developed to conquer the adverse consequences of ErbB2 overexpression such as **paclitaxel** resistance. Among these, trastuzumab has brought great promise. We have recently shown that trastuzumab can effectively sensitize ErbB2-overexpressing breast **cancer** cells to **paclitaxel** by reversing the antiapoptotic function of ErbB2. Our studies provide additional support for chemotherapy combined with trastuzumab for ErbB2-overexpressing breast **cancers**, and it may bring insights into designing more effective and specific therapies that could offer great benefits to patients. Copyright 2001. . .

CT . . . Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Animals
*Antibodies, Monoclonal: PD, pharmacology
*Antineoplastic Agents: PD, pharmacology
Apoptosis
***Breast Neoplasms: DT, drug therapy**
***Breast Neoplasms: GE, genetics**
Breast Neoplasms: ME, metabolism
***Drug Resistance, Neoplasm**
Drug Resistance, Neoplasm: GE, genetics
Gene Expression
*Genes, erbB-2
***Paclitaxel: PD, pharmacology**
Receptor, erbB-2

RN **33069-62-4 (Paclitaxel)**

L8 ANSWER 6 OF 27 MEDLINE on STN

AB PURPOSE: Epidermal growth factor receptor (EGFR) and other members of the **ErbB** family of receptor **tyrosine kinases** (RTK) mediate autocrine growth regulation in a wide spectrum of human **tumor** cells. We have previously demonstrated that in stably transfected mammary **carcinoma** cells a dominant negative (DN) mutant of EGFR, EGFR-CD533 is a potent inhibitor of EGFR and its cytoprotective signaling after exposure to ionizing **radiation**. In the present study, we further investigate the capacity of a genetic approach, using replication-incompetent adenovirus (Ad)-mediated transfer of EGFR-CD533 (Ad-EGFR-CD533), to enhance the radiosensitivity in vitro of four cell lines representative of three major **cancer** phenotypes. METHODS AND MATERIALS: The cell lines MDA-MB-231 and T-47D mammary **carcinoma**, A-431 squamous **carcinoma**, and U-373 MG malignant **glioma** cells were used. The **ErbB** expression profiles and the EGFR **tyrosine** phosphorylation (Tyr-P) levels following irradiation were quantified by Western blotting. The relative radiosensitivities of **tumor** cells were assessed by standard colony formation assays after infection with control vector (Ad-LacZ) or Ad-EGFR-CD533. RESULTS: The expression profiles demonstrated varying levels of EGFR, ErbB2, ErbB3, and ErbB4 expression. The overexpression of EGFR-CD533 after infection with Ad-EGFR-CD533 completely inhibited the **radiation**-induced stimulation of EGFR Tyr-P relative to the

immediate 2.4- to 3.1-fold increases in EGFR Tyr-P in control infected cells (Ad-LacZ). Ad-EGFR-CD533-infected cells demonstrated significant ($p < 0.001$) radiosensitization over a range of **radiation** doses (1-8 Gy), yielding dose-enhancement ratios (DER) between 1.4 and 1.7. This radiosensitization was maintained under conditions of repeated **radiation** exposures, using 3 x 2 Gy, yielding DERs of 1.6 and 1.7 for MDA-MB-231 and U-373 cells, respectively. CONCLUSIONS: Overexpression of EGFR-CD533 significantly sensitizes human **carcinoma** and **glioma** cells to single and repeated **radiation** exposures irrespective of their **ErbB** expression levels. Therefore, transduction of human **tumor** cells with EGFR-CD533 holds promise as a gene therapeutic approach for the radiosensitization of **neoplastic** cells that are growth-regulated by EGFR or other **ErbB** receptors.

ACCESSION NUMBER: 2001644761 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11697324
TITLE: Adenovirus-mediated overexpression of dominant negative epidermal growth factor receptor-CD533 as a gene therapeutic approach radiosensitizes human **carcinoma** and malignant **glioma** cells.
AUTHOR: Lammering G; Lin P S; Contessa J N; Hampton J L; Valerie K; Schmidt-Ullrich R K
CORPORATE SOURCE: Department of Radiation Oncology, Medical College of Virginia, Virginia Commonwealth University, Richmond 23298-0058, USA.
CONTRACT NUMBER: PO1 CA72955 (NCI)
R01 CA65896 (NCI)
SOURCE: International journal of radiation oncology, biology, physics, **(2001 Nov 1)** 51 (3) 775-84.
Journal code: 7603616. ISSN: 0360-3016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011108
Last Updated on STN: 20020123
Entered Medline: 20011204

TI Adenovirus-mediated overexpression of dominant negative epidermal growth factor receptor-CD533 as a gene therapeutic approach radiosensitizes human **carcinoma** and malignant **glioma** cells.

SO International journal of radiation oncology, biology, physics, **(2001 Nov 1)** 51 (3) 775-84.
Journal code: 7603616. ISSN: 0360-3016.

AB PURPOSE: Epidermal growth factor receptor (EGFR) and other members of the **ErbB** family of receptor **tyrosine kinases** (RTK) mediate autocrine growth regulation in a wide spectrum of human **tumor** cells. We have previously demonstrated that in stably transfected mammary **carcinoma** cells a dominant negative (DN) mutant of EGFR, EGFR-CD533 is a potent inhibitor of EGFR and its cytoprotective signaling after exposure to ionizing **radiation**. In the present study, we further investigate the capacity of a genetic approach, using replication-incompetent adenovirus (Ad)-mediated transfer of EGFR-CD533 (Ad-EGFR-CD533), to enhance the radiosensitivity in vitro of four cell lines representative of three major **cancer** phenotypes. METHODS AND MATERIALS: The cell lines MDA-MB-231 and T-47D mammary **carcinoma**, A-431 squamous **carcinoma**, and U-373 MG

malignant **glioma** cells were used. The **ErbB** expression profiles and the EGFR **tyrosine** phosphorylation (Tyr-P) levels following irradiation were quantified by Western blotting. The relative radiosensitivities of **tumor** cells were assessed by standard colony formation assays after infection with control vector (Ad-LacZ) or Ad-EGFR-CD533. RESULTS: The expression profiles. . . varying levels of EGFR, ErbB2, ErbB3, and ErbB4 expression. The overexpression of EGFR-CD533 after infection with Ad-EGFR-CD533 completely inhibited the **radiation**-induced stimulation of EGFR Tyr-P relative to the immediate 2.4- to 3.1-fold increases in EGFR Tyr-P in control infected cells (Ad-LacZ). Ad-EGFR-CD533-infected cells demonstrated significant ($p < 0.001$) radiosensitization over a range of **radiation** doses (1-8 Gy), yielding dose-enhancement ratios (DER) between 1.4 and 1.7. This radiosensitization was maintained under conditions of repeated **radiation** exposures, using 3 x 2 Gy, yielding DERs of 1.6 and 1.7 for MDA-MB-231 and U-373 cells, respectively. CONCLUSIONS: Overexpression of EGFR-CD533 significantly sensitizes human **carcinoma** and **glioma** cells to single and repeated **radiation** exposures irrespective of their **ErbB** expression levels. Therefore, transduction of human **tumor** cells with EGFR-CD533 holds promise as a gene therapeutic approach for the radiosensitization of **neoplastic** cells that are growth-regulated by EGFR or other **ErbB** receptors.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adenoviridae: GE, genetics
Breast Neoplasms: GE, genetics
***Breast Neoplasms: ME, metabolism**
Breast Neoplasms: TH, therapy
Carcinoma, Squamous Cell: GE, genetics
***Carcinoma, Squamous Cell: ME, metabolism**
Carcinoma, Squamous Cell: TH, therapy
Gene Expression Regulation, Neoplastic
*Gene Therapy: MT, methods
Genes, Dominant
Glioma: GE, genetics
***Glioma: ME, metabolism**
Glioma: TH, therapy
Phosphorylation
Radiation Tolerance
Receptor, Epidermal Growth Factor: GE, genetics
*Receptor, Epidermal Growth Factor: ME, metabolism
Receptor, erbB-2: GE, genetics
*Receptor, erbB-2: ME, metabolism
Receptor, erbB-3: GE, genetics
*Receptor, erbB-3: ME, metabolism
Tumor Cells, Cultured: RE, radiation effects
Tumor Stem Cell Assay

L8 ANSWER 7 OF 27 MEDLINE on STN

AB The **ErbB** receptor family is implicated in the malignant transformation of several **tumor** types and is overexpressed frequently in breast, ovarian, and other **tumors**. The mechanism by which CI-1033 and **gemcitabine**, either singly or in combination, kill **tumor** cells was examined in two breast lines, MDA-MB-453 and BT474; both overexpress the **ErbB**-2 receptor. CI-1033, a potent inhibitor of the **ErbB** family of receptor **tyrosine kinases**, reduced levels of activated Akt in

MDA-MB-453 cells. This effect alone, however, did not induce apoptosis in these cells. **Gemcitabine** treatment resulted in a moderate increase in the percentage of apoptotic cells that was accompanied by activation of p38 and MAPK (ERK1/2). CI-1033 given 24 h after **gemcitabine** produced a significant increase in the apoptotic fraction over treatment with either drug alone. During the combined treatment p38 remained activated, whereas Akt and activated MAPK were suppressed. Substitution of CI-1033 with the phosphatidylinositol 3-**kinase** inhibitor LY294002 and the MAPK/ERK **kinase** inhibitor PD 098059 in combination with **gemcitabine** produced the same results as the combination of CI-1033 and **gemcitabine**. p38 suppression by SB203580 prevented the enhanced cell kill by CI-1033. In contrast to MDA-MB-453, BT474 cells exhibited activated p38 under unstressed conditions as well as activated Akt and MAPK. Treatment of BT474 cells with CI-1033 inhibited both the phosphorylation of Akt and MAPK and resulted in a 47% apoptotic fraction. **Gemcitabine** did not cause apoptosis in the BT474 cells. These data indicate that suppression of Akt and MAPK in the presence of activated p38 results in cell death and a possible mechanism for the enhanced apoptosis produced by the combination of CI-1033 and **gemcitabine** in MDA-MB-453 cells. Furthermore, **tumors** that depend on **ErbB** receptor signaling for survival and exhibit activated p38 in the basal state may be susceptible to apoptosis by CI-1033 as a single agent.

ACCESSION NUMBER: 2001370796 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11278435
TITLE: Akt, MAPK (Erk1/2), and p38 act in concert to promote apoptosis in response to ErbB receptor family inhibition.
AUTHOR: Nelson J M; Fry D W
CORPORATE SOURCE: Pfizer Global Research and Development, Ann Arbor, Michigan 48105, USA.. James.Nelson@Pfizer.com
SOURCE: Journal of biological chemistry, **(2001 May 4)** 276 (18) 14842-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010702
Last Updated on STN: 20030105
Entered Medline: 20010628

SO Journal of biological chemistry, **(2001 May 4)** 276 (18) 14842-7.
Journal code: 2985121R. ISSN: 0021-9258.

AB The **ErbB** receptor family is implicated in the malignant transformation of several **tumor** types and is overexpressed frequently in breast, ovarian, and other **tumors**. The mechanism by which CI-1033 and **gemcitabine**, either singly or in combination, kill **tumor** cells was examined in two breast lines, MDA-MB-453 and BT474; both overexpress the **ErbB**-2 receptor. CI-1033, a potent inhibitor of the **ErbB** family of receptor **tyrosine kinases**, reduced levels of activated Akt in MDA-MB-453 cells. This effect alone, however, did not induce apoptosis in these cells. **Gemcitabine** treatment resulted in a moderate increase in the percentage of apoptotic cells that was accompanied by activation of p38 and MAPK (ERK1/2). CI-1033 given 24 h after **gemcitabine** produced a significant increase in the apoptotic fraction over treatment with either drug alone. During the combined

treatment p38 remained activated, whereas Akt and activated MAPK were suppressed. Substitution of CI-1033 with the phosphatidylinositol 3-**kinase** inhibitor LY294002 and the MAPK/ERK **kinase** inhibitor PD 098059 in combination with **gemcitabine** produced the same results as the combination of CI-1033 and **gemcitabine**. p38 suppression by SB203580 prevented the enhanced cell kill by CI-1033. In contrast to MDA-MB-453, BT474 cells exhibited activated p38. . . of BT474 cells with CI-1033 inhibited both the phosphorylation of Akt and MAPK and resulted in a 47% apoptotic fraction. **Gemcitabine** did not cause apoptosis in the BT474 cells. These data indicate that suppression of Akt and MAPK in the presence. . . p38 results in cell death and a possible mechanism for the enhanced apoptosis produced by the combination of CI-1033 and **gemcitabine** in MDA-MB-453 cells. Furthermore, **tumors** that depend on **ErbB** receptor signaling for survival and exhibit activated p38 in the basal state may be susceptible to apoptosis by CI-1033 as. . .

CT . . .

AI, antagonists & inhibitors
*Protein Kinases: ME, metabolism
Receptor Protein-Tyrosine Kinases: AI, antagonists & inhibitors
*Receptor Protein-Tyrosine Kinases: ME, metabolism
Tumor Cells, Cultured

RN **103882-84-4 (gemcitabine)**; 154447-36-6 (2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one); 289499-45-2 (CI1033); 951-77-9 (Deoxycytidine)

L8 ANSWER 8 OF 27 MEDLINE on STN

AB BACKGROUND: The c-**erbB**-2 oncogene encodes a transmembrane **tyrosine kinase** receptor and its abnormal expression may be related to the prognosis of gastric **cancer**. Gastric **cancer** is relatively resistant to various drugs, including **cisplatin**. **Cisplatin** is widely used in **cancer** chemotherapy, but the mechanisms of drug resistance are not yet known. METHODS: We used the human gastric **cancer** cell lines MKN-7 and KATO-III, which express the c-**erbB**-2 oncogene, as a model for relative resistance to **cisplatin**. We investigated whether inhibition with antisense oligonucleotides against c-**erbB**-2 increased the sensitivity of MKN-7 and KATO-III cells to **cisplatin**. Results: Antisense oligonucleotides for c-**erbB**-2 inhibited the expression of c-**erbB**-2 mRNA and protein and increased sensitivity to **cisplatin**, but not to other drugs, in MKN-7 and KATO-III cells. Cell growth was also inhibited by c-**erbB**-2 antisense oligonucleotides but not sense oligonucleotides. CONCLUSION: These findings indicate that c-**erbB**-2 expression in gastric **cancer** is one of the factors related to **cisplatin** sensitivity, and that anti-c-**erbB**-2 antisense oligonucleotides induced increased sensitivity to **cisplatin**.

ACCESSION NUMBER: 2001332351 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11399867
TITLE: Increased sensitivity to **cisplatin** in gastric **cancer** by antisense inhibition of the her-2/neu (c-erbB-2) gene.
AUTHOR: Funato T; Kozawa K; Fujimaki S; Miura T; Kaku M
CORPORATE SOURCE: Division of Molecular Diagnostics, Department of Clinical Medicine, Tohoku University School of Medicine, Sendai, Japan.. tfunato@mail.cc.tohoku.ac.jp
SOURCE: Chemotherapy, **(2001 Jul-Aug)** 47 (4) 297-303.

Journal code: 0144731. ISSN: 0009-3157.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

TI Increased sensitivity to **cisplatin** in gastric **cancer** by antisense inhibition of the her-2/neu (c-erbB-2) gene.

SO Chemotherapy, **(2001 Jul-Aug)** 47 (4) 297-303.
Journal code: 0144731. ISSN: 0009-3157.

AB BACKGROUND: The c-**erbB**-2 oncogene encodes a transmembrane **tyrosine kinase** receptor and its abnormal expression may be related to the prognosis of gastric **cancer**. Gastric **cancer** is relatively resistant to various drugs, including **cisplatin**. **Cisplatin** is widely used in **cancer** chemotherapy, but the mechanisms of drug resistance are not yet known. METHODS: We used the human gastric **cancer** cell lines MKN-7 and KATO-III, which express the c-**erbB**-2 oncogene, as a model for relative resistance to **cisplatin**. We investigated whether inhibition with antisense oligonucleotides against c-**erbB**-2 increased the sensitivity of MKN-7 and KATO-III cells to **cisplatin**. Results: Antisense oligonucleotides for c-**erbB**-2 inhibited the expression of c-**erbB**-2 mRNA and protein and increased sensitivity to **cisplatin**, but not to other drugs, in MKN-7 and KATO-III cells. Cell growth was also inhibited by c-**erbB**-2 antisense oligonucleotides but not sense oligonucleotides. CONCLUSION: These findings indicate that c-**erbB**-2 expression in gastric **cancer** is one of the factors related to **cisplatin** sensitivity, and that anti-c-**erbB**-2 antisense oligonucleotides induced increased sensitivity to **cisplatin**.

CT Check Tags: Human
*Antineoplastic Agents: PD, pharmacology
***Cisplatin: PD, pharmacology**
*Genes, erbB-2: DE, drug effects
Genes, erbB-2: PH, physiology
Neoplasm Proteins: ME, metabolism
*Oligonucleotides, Antisense: PD, pharmacology
Oncogene Proteins v-erbB: ME, metabolism
***Stomach Neoplasms: DT, drug therapy**
Stomach Neoplasms: GE, genetics
Tumor Cells, Cultured

RN **15663-27-1 (Cisplatin)**

CN 0 (Antineoplastic Agents); 0 (**Neoplasm** Proteins); 0 (Oligonucleotides, Antisense); 0 (Oncogene Proteins v-erbB)

L8 ANSWER 9 OF 27 MEDLINE on STN

AB PURPOSE: Overexpression of the **ErbB** family of growth factor receptors is present in a wide variety of human **tumors** and is correlated with poor prognosis. The purpose of this study was to determine the effects of a novel small molecule **ErbB** **tyrosine kinase** inhibitor, CI-1033, in combination with ionizing **radiation** on breast **cancer** cell growth and survival. MATERIALS & METHODS: Growth assays were performed on **ErbB**-overexpressing human breast **cancer** cells developed

in our laboratory in the presence of 0.1-1.0 microM CI-1033 (Parke Davis). Clonogenic survival assays were performed in the presence of ionizing **radiation** with or without CI-1033. For some experiments, clonogen numbers, defined as the product of surviving fraction and total number of cells, were calculated at each time point during a course of multifraction **radiation**. RESULTS: CI-1033 potently inhibited the growth of **ErbB**-overexpressing breast **cancer** cells. A single 48-h exposure of 1 microM CI-1033 resulted in growth inhibition for 7 days, whereas three times weekly administration resulted in sustained growth inhibition. Clonogenic survival was modestly decreased after a 7-day exposure to CI-1033. Exposure to both CI-1033 and **radiation** (6 Gy) yielded a 23-fold decrease in clonogenic survival compared to **radiation** alone. In a multifraction experiment, exposure to CI-1033 and three 5-Gy fractions of gamma **radiation** decreased the total number of clonogens in the population by 65-fold compared to **radiation** alone. CONCLUSION: CI-1033 results in potent growth inhibition and modest cytotoxicity of **ErbB**-overexpressing breast **cancer** cells, and has synergistic effects when combined with ionizing **radiation**. These data suggest that CI-1033 may have excellent clinical potential both alone and in combination with **radiation** therapy.

ACCESSION NUMBER: 2001078126 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11121658
TITLE: Radiosensitization of human breast **cancer** cells by a novel **ErbB** family receptor **tyrosine kinase** inhibitor.
AUTHOR: Rao G S; Murray S; Ethier S P
CORPORATE SOURCE: Department of Radiation Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA.
CONTRACT NUMBER: CA70354 (NCI)
SOURCE: International journal of radiation oncology, biology, physics, **(2000 Dec 1)** 48 (5) 1519-28.
Journal code: 7603616. ISSN: 0360-3016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010111

TI Radiosensitization of human breast **cancer** cells by a novel **ErbB** family receptor **tyrosine kinase** inhibitor.

SO International journal of radiation oncology, biology, physics, **(2000 Dec 1)** 48 (5) 1519-28.
Journal code: 7603616. ISSN: 0360-3016.

AB PURPOSE: Overexpression of the **ErbB** family of growth factor receptors is present in a wide variety of human **tumors** and is correlated with poor prognosis. The purpose of this study was to determine the effects of a novel small molecule **ErbB** **tyrosine kinase** inhibitor, CI-1033, in combination with ionizing **radiation** on breast **cancer** cell growth and survival. MATERIALS & METHODS: Growth assays were performed on **ErbB**-overexpressing human breast **cancer** cells developed in our laboratory in the presence of 0.1-1.0 microM CI-1033 (Parke Davis). Clonogenic survival assays were performed in the presence of ionizing

radiation with or without CI-1033. For some experiments, clonogen numbers, defined as the product of surviving fraction and total number of cells, were calculated at each time point during a course of multifraction **radiation**. RESULTS: CI-1033 potently inhibited the growth of **ErbB**-overexpressing breast **cancer** cells. A single 48-h exposure of 1 microM CI-1033 resulted in growth inhibition for 7 days, whereas three times weekly. . . in sustained growth inhibition. Clonogenic survival was modestly decreased after a 7-day exposure to CI-1033. Exposure to both CI-1033 and **radiation** (6 Gy) yielded a 23-fold decrease in clonogenic survival compared to **radiation** alone. In a multifraction experiment, exposure to CI-1033 and three 5-Gy fractions of gamma **radiation** decreased the total number of clonogens in the population by 65-fold compared to **radiation** alone. CONCLUSION: CI-1033 results in potent growth inhibition and modest cytotoxicity of **ErbB**-overexpressing breast **cancer** cells, and has synergistic effects when combined with ionizing **radiation**. These data suggest that CI-1033 may have excellent clinical potential both alone and in combination with **radiation** therapy.

CT Check Tags: Female; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

Breast Neoplasms: ME, metabolism
Breast Neoplasms: PA, pathology
***Breast Neoplasms: RT, radiotherapy**
Cell Division: DE, drug effects
Cell Survival: RE, radiation effects
Dose Fractionation
*Enzyme Inhibitors: TU, therapeutic use
***Neoplasm Proteins: AI, antagonists & inhibitors**
Radiation Tolerance
***Radiation-Sensitizing Agents: TU, therapeutic use**
Receptor, Epidermal Growth Factor: ME, metabolism
*Receptor, erbB-2: AI, antagonists & inhibitors
Tumor Cells, Cultured: DE, drug effects
Tumor Cells, Cultured: RE, radiation effects
Tumor Stem Cell Assay

CN 0 (Enzyme Inhibitors); 0 (**Neoplasm** Proteins); 0 (**Radiation**-Sensitizing Agents); EC 2.7.1.112 (Receptor, Epidermal Growth Factor); EC 2.7.1.112 (Receptor, erbB-2)

L8 ANSWER 10 OF 27 MEDLINE on STN

AB Overexpression of the c-**erbB**-2/HER-2/neu protooncogene which encodes for the **tyrosine kinase** receptor p185neu, has been observed frequently in **cisplatin** resistant human **tumors**, such as colorectal, breast, and non-small-cell lung **cancers**, and is known to induce resistance to **cisplatin** (CDDP) in vitro. To confirm a direct relationship between **erbB** -2 expression and CDDP resistance, we examined the role of **erbB** -2 in the cellular sensitivity to **cisplatin** using **erbB** -2 transfected HAG-1 human gallbladder **adenocarcinoma** cell lines. Three out of four cell lines, which stably expressed **ErbB** -2 protein (p185neu), did not show CDDP resistance but acquired sensitivity to **cisplatin**, compared to non-transfected cells. This chemosensitivity appears to be inversely correlated with the abundance of p185neu. Although the mechanism still remains unclear, these results suggest that sensitivity to CDDP in **erbB**-2 expressed cells may vary, depending on the cell type.

ACCESSION NUMBER: 2000162643 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10697535
TITLE: Expression of activated c-erbB-2 oncogene induces sensitivity to **cisplatin** in human gallbladder **adenocarcinoma** cells.
AUTHOR: Boudny V; Murakami Y; Nakano S; Niho Y
CORPORATE SOURCE: First Department of Internal Medicine, Faculty of Medicine, Kyushu University, Fukuoka, Japan.
SOURCE: Anticancer research, **(1999 Nov-Dec)** 19 (6B) 5203-6.
Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000323

TI Expression of activated c-erbB-2 oncogene induces sensitivity to **cisplatin** in human gallbladder **adenocarcinoma** cells.

SO Anticancer research, **(1999 Nov-Dec)** 19 (6B) 5203-6.
Journal code: 8102988. ISSN: 0250-7005.

AB Overexpression of the c-**erbB**-2/HER-2/neu protooncogene which encodes for the **tyrosine kinase** receptor p185neu, has been observed frequently in **cisplatin** resistant human **tumors**, such as colorectal, breast, and non-small-cell lung **cancers**, and is known to induce resistance to **cisplatin** (CDDP) in vitro. To confirm a direct relationship between **erbB** -2 expression and CDDP resistance, we examined the role of **erbB** -2 in the cellular sensitivity to **cisplatin** using **erbB** -2 transfected HAG-1 human gallbladder **adenocarcinoma** cell lines. Three out of four cell lines, which stably expressed **ErbB** -2 protein (p185neu), did not show CDDP resistance but acquired sensitivity to **cisplatin**, compared to non-transfected cells. This chemosensitivity appears to be inversely correlated with the abundance of p185neu. Although the mechanism still remains unclear, these results suggest that sensitivity to CDDP in **erbB**-2 expressed cells may vary, depending on the cell type.

CT Check Tags: Human; Support, Non-U.S. Gov't
***Adenocarcinoma: DT, drug therapy**
Adenocarcinoma: GE, genetics
Adenocarcinoma: PA, pathology
*Antineoplastic Agents: PD, pharmacology
Antineoplastic Agents: TU, therapeutic use
***Cisplatin: PD, pharmacology**
Cisplatin: TU, therapeutic use
***Gallbladder Neoplasms: DT, drug therapy**
Gallbladder Neoplasms: GE, genetics
Gallbladder Neoplasms: PA, pathology
*Gene Expression
*Genes, erbB-2
Tumor Cells, Cultured

RN **15663-27-1 (Cisplatin)**

L8 ANSWER 11 OF 27 MEDLINE on STN

AB Overexpression of the c-**erbB**-2 (HER-2/neu) oncogene, which

encodes a transmembrane receptor **tyrosine kinase**, has been shown to be associated with poor prognosis in ovarian and breast **cancer**. Recent studies indicate that c-**erbB**-2 may also be involved in determining the chemosensitivity of human **cancers**. In the present study, we examined the role of c-**erbB**-2 for chemoresistance in ovarian **cancer**. Overexpression of c-**erbB**-2 mRNA in **tumor** tissue was associated with a shorter survival of patients with primary ovarian **cancer** (P = 0.0001; n = 77) and was an independent prognostic factor in the proportional-hazard model adjusted for International Federation of Gynecologists and Obstetricians stage, residual disease, chemotherapy, and age (P = 0.035). A significant association between expression of c-**erbB**-2 mRNA and survival was obtained for the subgroup of patients who received a standard chemotherapy with **carboplatin** or **cisplatin** and cyclophosphamide (P = 0.0003), whereas only a nonsignificant trend was observed for patients who did not receive a standard chemotherapy (P = 0.124). In addition, the application of a standard chemotherapy improved the survival of patients with relatively low c-**erbB**-2 expression (P = 0.013) but not of patients with overexpression of c-**erbB**-2 (P = 0.359). Expression of c-**erbB**-2 mRNA correlated with expression of topoisomerase IIalpha mRNA determined by a reverse semiquantitative PCR technique (P = 0.009), whereas expression of c-**erbB**-2 and topoisomerase IIbeta mRNA did not correlate (P = 0.221). To examine the hypothesis that coamplified and/or coregulated topoisomerase IIalpha contributes to the resistance of c-**erbB**-2-overexpressing **carcinomas**, we established a chemosensitivity assay using primary cells from an ovarian **carcinoma** that overexpressed both c-**erbB**-2 and topoisomerase IIalpha. The combination of **carboplatin** with nontoxic concentrations of the topoisomerase II inhibitors **etoposide** or novobiocin enhanced the toxicity of **carboplatin**. In contrast, the **tyrosine kinase** inhibitor emodin exhibited no chemosensitizing effect in cells of this individual **carcinoma**. In conclusion, overexpression of c-**erbB**-2 was associated with poor prognosis and poor response to chemotherapy. The data suggest that topoisomerase IIalpha, which correlates with c-**erbB**-2 expression, contributes to the resistance of c-**erbB**-2-overexpressing **carcinomas**.

ACCESSION NUMBER: 1999323396 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10397267
TITLE: Contribution of c-erbB-2 and topoisomerase IIalpha to chemoresistance in ovarian **cancer**.
AUTHOR: Hengstler J G; Lange J; Kett A; Dornhofer N; Meinert R; Arand M; Knapstein P G; Becker R; Oesch F; Tanner B
CORPORATE SOURCE: Institute of Toxicology, University of Mainz, Germany.. hengstle@mail.Uni-Mainz.de
SOURCE: Cancer research, **(1999 Jul 1)** 59 (13) 3206-14. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990806
Last Updated on STN: 20000303
Entered Medline: 19990728

TI Contribution of c-erbB-2 and topoisomerase IIalpha to chemoresistance in

ovarian **cancer**.

SO Cancer research, **(1999 Jul 1)** 59 (13) 3206-14.
Journal code: 2984705R. ISSN: 0008-5472.

AB Overexpression of the c-**erbB**-2 (HER-2/neu) oncogene, which encodes a transmembrane receptor **tyrosine kinase**, has been shown to be associated with poor prognosis in ovarian and breast **cancer**. Recent studies indicate that c-**erbB**-2 may also be involved in determining the chemosensitivity of human **cancers**. In the present study, we examined the role of c-**erbB**-2 for chemoresistance in ovarian **cancer**. Overexpression of c-**erbB**-2 mRNA in **tumor** tissue was associated with a shorter survival of patients with primary ovarian **cancer** (P = 0.0001; n = 77) and was an independent prognostic factor in the proportional-hazard model adjusted for International Federation of Gynecologists and Obstetricians stage, residual disease, chemotherapy, and age (P = 0.035). A significant association between expression of c-**erbB**-2 mRNA and survival was obtained for the subgroup of patients who received a standard chemotherapy with **carboplatin** or **cisplatin** and cyclophosphamide (P = 0.0003), whereas only a nonsignificant trend was observed for patients who did not receive a standard. . . chemotherapy (P = 0.124). In addition, the application of a standard chemotherapy improved the survival of patients with relatively low c-**erbB**-2 expression (P = 0.013) but not of patients with overexpression of c-**erbB**-2 (P = 0.359). Expression of c-**erbB**-2 mRNA correlated with expression of topoisomerase IIalpha mRNA determined by a reverse semiquantitative PCR technique (P = 0.009), whereas expression of c-**erbB**-2 and topoisomerase IIbeta mRNA did not correlate (P = 0.221). To examine the hypothesis that coamplified and/or coregulated topoisomerase IIalpha contributes to the resistance of c-**erbB**-2-overexpressing **carcinomas**, we established a chemosensitivity assay using primary cells from an ovarian **carcinoma** that overexpressed both c-**erbB**-2 and topoisomerase IIalpha. The combination of **carboplatin** with nontoxic concentrations of the topoisomerase II inhibitors **etoposide** or novobiocin enhanced the toxicity of **carboplatin**. In contrast, the **tyrosine kinase** inhibitor emodin exhibited no chemosensitizing effect in cells of this individual **carcinoma**. In conclusion, overexpression of c-**erbB**-2 was associated with poor prognosis and poor response to chemotherapy. The data suggest that topoisomerase IIalpha, which correlates with c-**erbB**-2 expression, contributes to the resistance of c-**erbB**-2-overexpressing **carcinomas**.

CT Check Tags: Female; Human; Support, Non-U.S. Gov't
*Antineoplastic Agents: TO, toxicity
Carboplatin: TO, toxicity
Cell Survival: DE, drug effects
DNA Primers
*DNA Topoisomerases, Type II: GE, genetics
*DNA Topoisomerases, Type II, Eukaryotic
***Drug Resistance, Neoplasm**
Etoposide: TO, toxicity
Follow-Up Studies
*Genes, erbB-2
*Isoenzymes: GE, genetics
Models, Biological
Neoplasm Proteins: GE, genetics
Neoplasm Staging

***Ovarian Neoplasms: GE, genetics**
Ovarian Neoplasms: MO, mortality
***Ovarian Neoplasms: PA, pathology**
Ovarian Neoplasms: SU, surgery
Polymerase Chain Reaction
RNA, Messenger: GE, genetics
*Receptor, erbB-2: GE, genetics
Survival Analysis
Time Factors
Transcription, Genetic
Tumor Cells, Cultured

RN **33419-42-0 (Etoposide); 41575-94-4 (Carboplatin)**
CN 0 (Antineoplastic Agents); 0 (DNA Primers); 0 (Isoenzymes); 0 (**Neoplasm** Proteins); 0 (RNA, Messenger); EC 2.7.1.112 (Receptor, erbB-2); EC 5.99.1.- (DNA Topoisomerases, Type II, Eukaryotic); EC 5.99.1.- (DNA topoisomerase II. . .

L8 ANSWER 12 OF 27 MEDLINE on STN
AB Overexpression of the **erbB**-2 **tyrosine kinase** receptor, p185erbB-2, is a common alteration in non-small cell lung **cancer** (NSCLC) and has been associated with poor prognosis and a **tumor** drug resistance phenotype. In this study, we have examined the consequences of **erbB**-2 depletion on DNA repair, cell cycle, and apoptosis using a panel of NSCLC cell lines constitutively overexpressing **erbB**-2 receptor. Depletion of the **erbB** -2 was achieved using the **tyrosine kinase** inhibitor CP127,374 which promotes **erbB**-2 degradation. Treatment with CP127,374 concentrations which deplete **erbB**-2 and inhibit **tyrosine** phosphorylation resulted in downregulation of DNA repair mechanisms and cell accumulation at G1 phase of the cell cycle. GI arrest was observed in cells with mutated p53 as well as cells lacking p53 protein, suggesting a p53-independent mechanisms. NSCLC cells which overexpress **erbB**-2 were more resistant to **cisplatin** -induced cytotoxicity in comparison to cells expressing low levels of **erbB**-2. Treatment with CP127,374 alone did not result in any induction of apoptosis. A combination of CP127,374 and **cisplatin** , however, was more potent in cell growth inhibition and induction of apoptosis compared to treatment with **cisplatin** alone. Together, our results further support a pivotal role of **erbB**-2 signaling in the regulatory balance between DNA repair, cell cycle checkpoints and apoptosis; all these mechanisms are essential determinants for **tumor** cell destiny following chemotherapy stress.

ACCESSION NUMBER: 1999087338 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9872333
TITLE: Dual effect of erbB-2 depletion on the regulation of DNA repair and cell cycle mechanisms in non-small cell lung **cancer** cells.
AUTHOR: You X L; Yen L; Zeng-Rong N; Al Moustafa A E; Alaoui-Jamali M A
CORPORATE SOURCE: Lady Davis Institute of the Sir Mortimer B Davis Jewish General Hospital, Department of Medicine and McGill Centre for Translational Research in Cancer, McGill University, Montreal, Quebec, Canada.
SOURCE: Oncogene, **(1998 Dec 17)** 17 (24) 3177-86. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 20000303
Entered Medline: 19990126

TI Dual effect of erbB-2 depletion on the regulation of DNA repair and cell cycle mechanisms in non-small cell lung **cancer** cells.

SO Oncogene, **(1998 Dec 17)** 17 (24) 3177-86.
Journal code: 8711562. ISSN: 0950-9232.

AB Overexpression of the **erbB**-2 **tyrosine kinase** receptor, p185erbB-2, is a common alteration in non-small cell lung **cancer** (NSCLC) and has been associated with poor prognosis and a **tumor** drug resistance phenotype. In this study, we have examined the consequences of **erbB**-2 depletion on DNA repair, cell cycle, and apoptosis using a panel of NSCLC cell lines constitutively overexpressing **erbB**-2 receptor. Depletion of the **erbB** -2 was achieved using the **tyrosine kinase** inhibitor CP127,374 which promotes **erbB**-2 degradation. Treatment with CP127,374 concentrations which deplete **erbB**-2 and inhibit **tyrosine** phosphorylation resulted in downregulation of DNA repair mechanisms and cell accumulation at G1 phase of the cell cycle. GI arrest. . . in cells with mutated p53 as well as cells lacking p53 protein, suggesting a p53-independent mechanisms. NSCLC cells which overexpress **erbB**-2 were more resistant to **cisplatin** -induced cytotoxicity in comparison to cells expressing low levels of **erbB**-2. Treatment with CP127,374 alone did not result in any induction of apoptosis. A combination of CP127,374 and **cisplatin** , however, was more potent in cell growth inhibition and induction of apoptosis compared to treatment with **cisplatin** alone. Together, our results further support a pivotal role of **erbB**-2 signaling in the regulatory balance between DNA repair, cell cycle checkpoints and apoptosis; all these mechanisms are essential determinants for **tumor** cell destiny following chemotherapy stress.

CT Check Tags: Human; Support, Non-U.S. Gov't
*Apoptosis
Carcinoma, Non-Small-Cell Lung
Cell Cycle
Cell Division: DE, drug effects
Cisplatin: PD, pharmacology
DNA Damage: DE, drug effects
*DNA Repair
Enzyme Inhibitors: PD, pharmacology
Lung Neoplasms
Quinones: PD, pharmacology
*Receptor, erbB-2: AI, antagonists & inhibitors
Receptor, erbB-2: BI, biosynthesis
Receptor, erbB-2: GE, genetics
Tumor Cells, Cultured

RN **15663-27-1 (Cisplatin)**

L8 ANSWER 13 OF 27 MEDLINE on STN

AB Several studies have suggested that biochemical or molecular markers examined in non-small cell lung **cancer** carry prognostic or treatment response information. Non-small cell lung **cancer** patients whose **tumors** have neuroendocrine (NE) features may be more responsive to chemotherapy. In addition, increased expression of

HER2 (c-**erbB**-2), a membrane-bound receptor with **tyrosine kinase** activity, has been associated with shortened survival. The **Cancer** and **Leukemia** Group B (CALGB) performed a study of patients with stage IIIA (N2 nodes positive) non-small cell lung **cancer** in which patients received initial chemotherapy followed by surgery, then post-operative therapy consisting of sequential chemotherapy and **radiation** therapy. Since all patients underwent mediastinoscopy, this provided an opportunity to compare pre- and post-chemotherapy **tumor** specimens to test the hypothesis that these proteins would predict treatment response. In particular, we hypothesized that the post-chemotherapy specimens would be enriched for NE marker negative cells because of the increased sensitivity of NE positive cells to chemotherapy. We performed immunohistochemical analysis for a panel of NE markers [neuron-specific enolase (NSE), Leu-7, chromogranin A (ChrA), synaptophysin (Syn)], HER2 and CEA to determine if there was an effect of therapy on the percentage of cells expressing these markers. Secondary endpoints were a correlation with chemotherapy response and survival. Slides were scored for intensity (0-4) and percentage of cells positive (0-4). Of 61 eligible patients, there were 38 with both pre- and post-chemotherapy specimens. When both intensity of staining and percentage of positive cells were considered, post-chemotherapy specimens had a higher percentage of positive NE markers compared with pre-chemotherapy. In addition, there was no correlation between NE marker, HER2 or CEA expression (prior to or post treatment) and response to chemotherapy or survival. These data do not support the hypothesis that NE positive **tumor** cells are preferentially killed by chemotherapy in patients with stage IIIA non-small cell lung **cancer.**

ACCESSION NUMBER: 1999073709 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9857998
TITLE: Analysis of neuroendocrine markers, HER2 and CEA before and after chemotherapy in patients with stage IIIA non-small cell lung **cancer**: a **Cancer** and **Leukemia** Group B study.
AUTHOR: Graziano S L; Kern J A; Herndon J E; Tatum A; Brisson M L; Memoli V; Sugarbaker D; Skarin A T; Kreisman H; Green M R
CORPORATE SOURCE: Department of Medicine, SUNY-Health Science Center and Veterans Affairs Medical Center, Syracuse, NY 13210, USA.
CONTRACT NUMBER: CA21060 (NCI)
CA33601 (NCI)
CA47642 (NCI)
+
SOURCE: Lung cancer (Amsterdam, Netherlands), **(1998 Sep)** 21 (3) 203-11.
Journal code: 8800805. ISSN: 0169-5002.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990311
Last Updated on STN: 20000303
Entered Medline: 19990225

TI Analysis of neuroendocrine markers, HER2 and CEA before and after chemotherapy in patients with stage IIIA non-small cell lung

cancer: a **Cancer** and **Leukemia** Group B study.
SO Lung cancer (Amsterdam, Netherlands), **(1998 Sep)** 21 (3) 203-11.
Journal code: 8800805. ISSN: 0169-5002.
AB Several studies have suggested that biochemical or molecular markers examined in non-small cell lung **cancer** carry prognostic or treatment response information. Non-small cell lung **cancer** patients whose **tumors** have neuroendocrine (NE) features may be more responsive to chemotherapy. In addition, increased expression of HER2 (c-**erbB**-2), a membrane-bound receptor with **tyrosine kinase** activity, has been associated with shortened survival. The **Cancer** and **Leukemia** Group B (CALGB) performed a study of patients with stage IIIA (N2 nodes positive) non-small cell lung **cancer** in which patients received initial chemotherapy followed by surgery, then post-operative therapy consisting of sequential chemotherapy and **radiation** therapy. Since all patients underwent mediastinoscopy, this provided an opportunity to compare pre- and post-chemotherapy **tumor** specimens to test the hypothesis that these proteins would predict treatment response. In particular, we hypothesized that the post-chemotherapy specimens. . . to or post treatment) and response to chemotherapy or survival. These data do not support the hypothesis that NE positive **tumor** cells are preferentially killed by chemotherapy in patients with stage IIIA non-small cell lung **cancer**.
CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
*Carcinoembryonic Antigen: AN, analysis
***Carcinoma, Non-Small-Cell Lung: CH, chemistry**
Carcinoma, Non-Small-Cell Lung: DI, diagnosis
Carcinoma, Non-Small-Cell Lung: DT, drug therapy
Carcinoma, Non-Small-Cell Lung: SU, surgery
Combined Modality Therapy
***Lung Neoplasms: CH, chemistry**
Lung Neoplasms: DI, diagnosis
Lung Neoplasms: DT, drug therapy
Lung Neoplasms: SU, surgery
Neoplasm Staging
Prognosis
*Receptor, erbB-2: AN, analysis
***Tumor Markers, Biological: AN, analysis**
CN 0 (Carcinoembryonic Antigen); 0 (**Tumor** Markers, Biological); EC 2.7.1.112 (Receptor, erbB-2)

L8 ANSWER 14 OF 27 MEDLINE on STN
AB The **erbB** family of **tyrosine kinase** receptors is involved in the regulation of a variety of vital functions including cell proliferation, cell differentiation, and stress response. Alteration in the expression of **erbB** receptors occurs in numerous **tumor** types and plays an important role in **cancer** development, **cancer** progression, and susceptibility to cell killing by anticancer agents. Of particular interest is the intrinsic drug resistance associated with overexpression of the **erbB**-2 receptor. In general, **tumor** cells overexpressing **erbB** -2 are intrinsically resistant to DNA-damaging agents such as **cisplatin**. While the molecular mechanisms by which **erbB** -2 induces drug resistance are not yet established, there is evidence that this may be a consequence of altered cell cycle checkpoint and DNA repair mechanisms and dysregulation of apoptotic pathway(s). The apoptotic signal induced by many anticancer drugs originates at a receptor on the

cell membrane and is transduced through a signaling cascade to the nucleus. Drug-induced apoptosis is dependent on the balance between cell cycle checkpoints and DNA repair mechanisms. Blockade of **erbB**-2 signaling using **erbB**-2 antagonists, dominant negative mutants, or chemical inhibitors of **erbB**-2 **tyrosine kinase** activity induces cell cycle arrest, inhibits DNA repair, and (or) promotes apoptosis. Less understood are downstream signal transduction cascades by which **erbB**-2 affects these regulatory mechanisms. The diversity of **erbB** receptors results in an interconnected network of cell signaling pathways that determine **tumor** cell fate in response to chemotherapy stress. Further investigations on the role of **erbB**-coupled signaling in the regulation of stress responsive genes are critical to understand the mechanisms by which **tumor** cells escape cell death, and will contribute to the development of alternative therapeutic targets to overcome intrinsic drug resistance in clinical settings.

ACCESSION NUMBER: 1998152973 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9493954
TITLE: The role of **ErbB**-2 **tyrosine kinase** receptor in cellular intrinsic chemoresistance: mechanisms and implications.
AUTHOR: Alaoui-Jamali M A; Paterson J; Al Moustafa A E; Yen L
CORPORATE SOURCE: Lady Davis Institute of the Sir Mortimer B. Davis Jewish General Hospital, Department of Medicine, McGill University, Montreal, QC, Canada.. mdaj@musica.mcgill.ca
SOURCE: Biochemistry and cell biology = Biochimie et biologie cellulaire, **(1997)** 75 (4) 315-25. Ref: 138
Journal code: 8606068. ISSN: 0829-8211.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980410
Last Updated on STN: 20000303
Entered Medline: 19980330

TI The role of **ErbB**-2 **tyrosine kinase** receptor in cellular intrinsic chemoresistance: mechanisms and implications.

SO Biochemistry and cell biology = Biochimie et biologie cellulaire, **(1997)** 75 (4) 315-25. Ref: 138
Journal code: 8606068. ISSN: 0829-8211.

AB The **erbB** family of **tyrosine kinase** receptors is involved in the regulation of a variety of vital functions including cell proliferation, cell differentiation, and stress response. Alteration in the expression of **erbB** receptors occurs in numerous **tumor** types and plays an important role in **cancer** development, **cancer** progression, and susceptibility to cell killing by anticancer agents. Of particular interest is the intrinsic drug resistance associated with overexpression of the **erbB**-2 receptor. In general, **tumor** cells overexpressing **erbB** -2 are intrinsically resistant to DNA-damaging agents such as **cisplatin**. While the molecular mechanisms by which **erbB** -2 induces drug resistance are not yet established, there is evidence that this may be a consequence of altered cell cycle. . . to the nucleus. Drug-induced apoptosis is dependent on the balance between cell cycle

checkpoints and DNA repair mechanisms. Blockade of **erbB**-2 signaling using **erbB**-2 antagonists, dominant negative mutants, or chemical inhibitors of **erbB**-2 **tyrosine kinase** activity induces cell cycle arrest, inhibits DNA repair, and (or) promotes apoptosis. Less understood are downstream signal transduction cascades by which **erbB**-2 affects these regulatory mechanisms. The diversity of **erbB** receptors results in an interconnected network of cell signaling pathways that determine **tumor** cell fate in response to chemotherapy stress. Further investigations on the role of **erbB**-coupled signaling in the regulation of stress responsive genes are critical to understand the mechanisms by which **tumor** cells escape cell death, and will contribute to the development of alternative therapeutic targets to overcome intrinsic drug resistance in. . .

CT Check Tags: Human; Support, Non-U.S. Gov't
Animals
***Drug Resistance, Neoplasm: PH, physiology**
*Receptor, erbB-2: PH, physiology

L8 ANSWER 15 OF 27 MEDLINE on STN

AB The c-**erbB**-2 (HER-2/neu) protooncogene encodes an M(r) 185,000 transmembrane glycoprotein with intrinsic **tyrosine kinase** activity. Agonistic antibodies against p185c-**erbB**-2 enhance the cytotoxic effect of the DNA alkylator, **cisplatin**, against c-**erbB**-2-overexpressing human **carcinoma** cells (Hancock et al., **Cancer** Res., 51:4575-4580, 1991). We have studied the possible association between receptor signal transduction and **cisplatin**-mediated cytotoxicity utilizing the SKBR-3 human breast **cancer** cell line and the anti-p185 TAb 250 IgG1. TAb 250 induced **tyrosine** phosphorylation of p185 and the receptor substrate phospholipase C-gamma 1, as well as rapid association of these molecules in vivo. Simultaneously with phosphorylation, phospholipase C-gamma 1 catalytic activity measured in a [3H]phosphatidylinositol-4,5-bisphosphate hydrolysis assay was increased 61 +/- 12% above control. Preincubation of SKBR-3 cells with the **tyrosine kinase** inhibitor tyrphostin 50864-2 abrogated the enhancement of drug-mediated cell kill induced by TAb 250. The supraadditive drug/antibody effect was not seen in SKBR-3 cells with TAb 263, an anti-p185 IgG1 that does not induce receptor signaling or with TAb 250 in MDA-468 breast **cancer** cells which do not overexpress c-**erbB**-2. In addition, transforming growth factor-alpha increased **cisplatin**-induced cytotoxicity against NIH 3T3 cells overexpressing an epidermal growth factor receptor/c-**erbB**-2 chimera. Cellular uptake or efflux of [195mPt]**cisplatin** by SKBR-3 cells was not altered by TAb 250. Finally, simultaneous treatment of SKBR-3 cells with TAb 250 and **cisplatin** increased **cisplatin**/DNA intrastrand adduct formation and delayed the rate of adduct decay. Taken together these data support a direct association between p185c-**erbB**-2 signal transduction and inhibition of **cisplatin**-induced DNA repair.

ACCESSION NUMBER: 94306382 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7913407
TITLE: p185c-**erbB**-2 signal enhances **cisplatin**-induced cytotoxicity in human breast **carcinoma** cells: association between an oncogenic receptor **tyrosine kinase** and drug-induced DNA repair.
AUTHOR: Arteaga C L; Winnier A R; Poirier M C; Lopez-Larraza D M;

Shawver L K; Hurd S D; Stewart S J
CORPORATE SOURCE: Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee.
SOURCE: Cancer research, **(1994 Jul 15)** 54 (14) 3758-65.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940825
Last Updated on STN: 20000303
Entered Medline: 19940816

TI p185c-**erbB**-2 signal enhances **cisplatin**-induced cytotoxicity in human breast **carcinoma** cells: association between an oncogenic receptor **tyrosine kinase** and drug-induced DNA repair.

SO Cancer research, **(1994 Jul 15)** 54 (14) 3758-65.
Journal code: 2984705R. ISSN: 0008-5472.

AB The c-**erbB**-2 (HER-2/neu) protooncogene encodes an M(r) 185,000 transmembrane glycoprotein with intrinsic **tyrosine kinase** activity. Agonistic antibodies against p185c-**erbB**-2 enhance the cytotoxic effect of the DNA alkylator, **cisplatin**, against c-**erbB**-2-overexpressing human **carcinoma** cells (Hancock et al., **Cancer** Res., 51:4575-4580, 1991). We have studied the possible association between receptor signal transduction and **cisplatin**-mediated cytotoxicity utilizing the SKBR-3 human breast **cancer** cell line and the anti-p185 TAb 250 IgG1. TAb 250 induced **tyrosine** phosphorylation of p185 and the receptor substrate phospholipase C-gamma 1, as well as rapid association of these molecules in vivo.. . . activity measured in a [3H]phosphatidylinositol-4,5-bisphosphate hydrolysis assay was increased 61 +/- 12% above control. Preincubation of SKBR-3 cells with the **tyrosine kinase** inhibitor tyrphostin 50864-2 abrogated the enhancement of drug-mediated cell kill induced by TAb 250. The supraadditive drug/antibody effect was not. . . cells with TAb 263, an anti-p185 IgG1 that does not induce receptor signaling or with TAb 250 in MDA-468 breast **cancer** cells which do not overexpress c-**erbB**-2. In addition, transforming growth factor-alpha increased **cisplatin**-induced cytotoxicity against NIH 3T3 cells overexpressing an epidermal growth factor receptor/c-**erbB**-2 chimera. Cellular uptake or efflux of [195mPt]**cisplatin** by SKBR-3 cells was not altered by TAb 250. Finally, simultaneous treatment of SKBR-3 cells with TAb 250 and **cisplatin** increased **cisplatin**/DNA intrastrand adduct formation and delayed the rate of adduct decay. Taken together these data support a direct association between p185c-**erbB**-2 signal transduction and inhibition of **cisplatin**-induced DNA repair.

CT Check Tags: Female; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.

Antibodies, Monoclonal: IM, immunology
Breast Neoplasms: ME, metabolism
***Breast Neoplasms: PA, pathology**
Cisplatin: ME, metabolism
***Cisplatin: PD, pharmacology**
*DNA Repair: DE, drug effects
Phosphorylation
Protein Kinase C: PH, physiology

*Proto-Oncogene Proteins: PH, physiology
*Receptor Protein-Tyrosine Kinases: PH, physiology
*Receptor, Epidermal Growth Factor: PH, physiology
Receptor, erbB-2
*Signal Transduction: DE, drug effects
Tumor Cells, Cultured
RN **15663-27-1 (Cisplatin)**

L8 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AB The invention relates to a combination therapy for the treatment of **tumors** metastases comprising administration of anti-angiogenic agents and **tumor** necrosis factor alpha (TNFα) optionally together with other cytotoxic agents, such as interferon gamma (IFNγ) or chemotherapeutic agents such as anti-EGFR antibodies. The method and the pharmaceutical compns. comprising said agents can result in a synergistic potentiation of the **tumor** cell proliferation inhibition effect of each individual therapeutic agent, yielding more effective treatment than found by administering an individual component alone.

ACCESSION NUMBER: 2002:832648 HCAPLUS
DOCUMENT NUMBER: 137:333130
TITLE: Combination therapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases
INVENTOR(S): Grell, Matthias; Goodman, Simon; Ruegg, Curzio
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002085405	A2	20021031	WO 2002-EP4298	20020418 <--
WO 2002085405	A3	20031002		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1381384	A2	20040121	EP 2002-745238	20020418
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2002009114	A	20040713	BR 2002-9114	20020418
US 2004136949	A1	20040715	US 2003-475713	20031023
PRIORITY APPLN. INFO.:			EP 2001-109981 A	20010424
			WO 2002-EP4298 W	20020418

TI Combination therapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases
PI WO 2002085405 A2 **20021031**

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002085405	A2	20021031	WO 2002-EP4298	20020418 <--
	WO 2002085405	A3	20031002		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1381384	A2	20040121	EP 2002-745238	20020418
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	BR 2002009114	A	20040713	BR 2002-9114	20020418
	US 2004136949	A1	20040715	US 2003-475713	20031023

AB The invention relates to a combination therapy for the treatment of **tumors** metastases comprising administration of anti-angiogenic agents and **tumor** necrosis factor alpha (TNFα) optionally together with other cytotoxic agents, such as interferon gamma (IFNγ) or chemotherapeutic agents such as anti-EGFR antibodies. The method and the pharmaceutical compns. comprising said agents can result in a synergistic potentiation of the **tumor** cell proliferation inhibition effect of each individual therapeutic agent, yielding more effective treatment than found by administering an individual component. . .

ST angiogenesis inhibitor RGD peptide antitumor **tumor** metastasis TNF interferon

IT Cell adhesion molecules
RL: BSU (Biological study, unclassified); BIOL (Biological study) (ICAM-1 (intercellular adhesion mol. 1); combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (IκB (inhibitor of NF-κB); combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (NF-κB (nuclear factor of κ light chain gene enhancer in B-cells); combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)

IT Proteins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TRAIL (**tumor** necrosis factor-related apoptosis-inducing ligand); combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)

IT Integrins
Vascular endothelial growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (antagonist; combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)

IT Epidermal growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(anti-EGFR; combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)
IT Antibodies and Immunoglobulins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(anti-HER2; combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)
IT Angiogenesis inhibitors
Antitumor agents
Apoptosis
Immunotherapy
Sarcoma
Signal transduction, biological
Test kits
(combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)
IT Mdm2 protein
p53 (protein)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)
IT Antibodies and Immunoglobulins
Fas ligand
RGD peptides
Tumor necrosis factors
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)
IT Blood vessel
(endothelium; combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)
IT Cell proliferation
(inhibition; combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)
IT **Neoplasm**
(metastasis; combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)
IT Phosphorylation, biological
(protein; combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)
IT Drug interactions
(synergistic; combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)
IT Interferons
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(γ; combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)
IT 79079-06-4, **ErbB** receptor **tyrosine kinase**
142243-02-5, ERK 142805-58-1, Mek 148640-14-6, Protein kinase Akt
155215-87-5, JNK 165245-96-5, p38 Kinase 169592-56-7, Caspase-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)
IT 188968-51-6

RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)

IT 11056-06-7, Bleomycin 15663-27-1, **Cisplatin** 23214-92-8, Doxorubicin 33069-62-4, Taxol 95058-81-4, **Gemcitabine** 114977-28-5, **Docetaxel**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination chemotherapy using anti-angiogenic agents and TNF-α for the treatment of **tumor** metastases)

L8 ANSWER 17 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AB Disclosed are methods for treating proliferative diseases, especially breast **cancers**, comprising administering (1) a therapeutically effective amount of a liposomal anthracycline composition in association with (2) a therapeutically effective amount of an antibody directed against the extracellular domain of a growth factor receptor and optionally in association with (3) a therapeutically effective amount of an addnl. antineoplastic agent. For example, the method comprises (1) administering PEGylated liposomal doxorubicin composition, followed by (2) cyclophosphamide, and (2) Trastuzumab (antibody).

ACCESSION NUMBER: 2002:637550 HCAPLUS
DOCUMENT NUMBER: 137:174955
TITLE: Targeted anti-**tumor** drug delivery systems
INVENTOR(S): Emanuel, David J.; Tendler, Craig L.
PATENT ASSIGNEE(S): Schering Corporation, USA
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002064168	A1	20020822	WO 2002-US4113	20020208 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002151508	A1	20021017	US 2002-67448	20020205 <--
EP 1359942	A1	20031112	EP 2002-714873	20020208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004518717	T2	20040624	JP 2002-563960	20020208

PRIORITY APPLN. INFO.: US 2001-267807P P 20010209
WO 2002-US4113 W 20020208

TI Targeted anti-**tumor** drug delivery systems

PI WO 2002064168 A1 **20020822**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI WO 2002064168 A1 20020822 WO 2002-US4113 20020208 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2002151508 A1 20021017 US 2002-67448 20020205 <--
EP 1359942 A1 20031112 EP 2002-714873 20020208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
JP 2004518717 T2 20040624 JP 2002-563960 20020208

AB Disclosed are methods for treating proliferative diseases, especially breast **cancers**, comprising administering (1) a therapeutically effective amount of a liposomal anthracycline composition in association with (2) a therapeutically effective amount. . .

IT Bladder, **neoplasm**
(**carcinoma**; targeted anti-**tumor** drug delivery systems)
IT Intestine, **neoplasm**
(colon; targeted anti-**tumor** drug delivery systems)
IT **Neoplasm**
(epithelial; targeted anti-**tumor** drug delivery systems)
IT Thyroid gland, **neoplasm**
(follicle cell; targeted anti-**tumor** drug delivery systems)
IT Growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; targeted anti-**tumor** drug delivery systems)
IT Drug delivery systems
(liposomes; targeted anti-**tumor** drug delivery systems)
IT neu (receptor)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(monoclonal antibody to; targeted anti-**tumor** drug delivery systems)
IT **Leukemia**
(myelogenous; targeted anti-**tumor** drug delivery systems)
IT Phosphatidylcholines, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(soya, hydrogenated; targeted anti-**tumor** drug delivery systems)
IT Antitumor agents
Drug delivery systems
Human
Lung, **neoplasm**
Mammary gland, **neoplasm**
Melanoma
Myelodysplastic syndromes
Neuroglia, **neoplasm**
Ovary, **neoplasm**
Pancreas, **neoplasm**
Prostate gland, **neoplasm**
(targeted anti-**tumor** drug delivery systems)
IT Anthracyclines
Interferons

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted anti-**tumor** drug delivery systems)

IT Antibodies and Immunoglobulins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(to growth factor receptors; targeted anti-**tumor** drug delivery systems)

IT 137632-09-8, Protein **tyrosine kinase erbB**-2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(monoclonal antibody to; targeted anti-**tumor** drug delivery systems)

IT 50-18-0, Cyclophosphamide 51-21-8, 5-Fluorouracil 66-75-1, Uracil mustard 148-82-3, Melphalan 305-03-3, Chlorambucil 3778-73-2, Ifosfamide 10540-29-1, Tamoxifen 13311-84-7, Flutamide 15663-27-1, **Cisplatin** 23214-92-8, Caelyx 25316-40-9, Doxorubicin hydrochloride 33069-62-4, **Paclitaxel** 33419-42-0, **Etoposide** 41575-94-4, **Carboplatin** 53714-56-0, Leuprolide 75607-67-9, Fludarabine phosphate 85622-93-1, Temozolomide 89778-26-7, Toremifene 95058-81-4, **Gemcitabine** 100286-90-6, **CPT-11** 112809-51-5, Letrozole 114977-28-5, **Docetaxel** 120511-73-1, Anastrozole 125317-39-7, Navelbine 154361-50-9, **Capecitabine** 180288-69-1, Trastuzumab
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted anti-**tumor** drug delivery systems)

IT 57-88-5, Cholesterol, biological studies 247925-28-6
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted anti-**tumor** drug delivery systems)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 18 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AB The present invention relates to a method for identifying nucleic acid mols. functionally associated with a desired phenotype, such as **cancer** cell properties, including anti-apoptosis. The method, which allows for generation of expression profiles of genes associated with said desired phenotype, involves a mutagenesis and/or genome rearrangement step, followed by selection of cell clones displaying the desired phenotype. The invention also relates that the method involves the use of the following techniques: fluorescence-activated cell sorting (FACS); nucleic acid microarray (cDNA, genomic or oligonucleotide); protein array; two-dimensional gel electrophoresis; and/or mass spectrometry. The invention further relates that the disclosed method was used to identify genes, which are differentially expressed in apoptosis-sensitive and apoptosis-resistant cells. Specifically, the invention relates that apoptosis was induced in human cervix **carcinoma** cell line HeLa S3 by Fas activation. After the selection procedure, only a low number of living cells were present, which had a higher resistance against apoptosis than the parental cell line. MRNA was isolated from these surviving clones, and from the parental cell line, and transcribed into cDNA. CDNA microarray technol. was used to identify about 150-200 genes (cDNA/DNA mols.) that exhibited enhanced expression in apoptosis-resistant clones. The GenBank accession nos. of some of these cDNA/DNA mols. are provided, along with the products encoded by said mols. Still further, the invention relates that most of the apoptosis-associated genes encode protein phosphatases, and kinases. Finally, the invention relates that said

nucleic acid mols., and proteins encoded by mols., can be used as targets in diagnosis, therapeutics and drug screening, particularly for disorders associated with dysfunction of apoptotic processes, such as **tumors**.

ACCESSION NUMBER: 2002:615889 HCAPLUS
DOCUMENT NUMBER: 137:180730
TITLE: Human cDNA/DNA molecules and proteins encoded by them with enhanced expression in apoptosis-resistant cell clones, and use thereof in diagnosis, therapeutics and drug screening
INVENTOR(S): Ullrich, Axel; Abraham, Reimar
PATENT ASSIGNEE(S): Max-Planck-Gesellschaft zur Foerderung der Wissenschaften e.V., Germany
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002063037	A2	20020815	WO 2002-EP1073	20020201 <--
WO 2002063037	A3	20031002		
WO 2002063037	C2	20040219		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1364066	A2	20031126	EP 2002-718083	20020201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004517638	T2	20040617	JP 2002-562773	20020201
US 2004110177	A1	20040610	US 2003-470845	20030731
PRIORITY APPLN. INFO.:			US 2001-265631P P	20010202
			WO 2002-EP1073 W	20020201

PI WO 2002063037 A2 **20020815**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002063037	A2	20020815	WO 2002-EP1073	20020201 <--
WO 2002063037	A3	20031002		
WO 2002063037	C2	20040219		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

EP 1364066	A2	20031126	EP 2002-718083	20020201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004517638	T2	20040617	JP 2002-562773	20020201
US 2004110177	A1	20040610	US 2003-470845	20030731

AB The present invention relates to a method for identifying nucleic acid mols. functionally associated with a desired phenotype, such as **cancer** cell properties, including anti-apoptosis. The method, which allows for generation of expression profiles of genes associated with said desired phenotype,. . . which are differentially expressed in apoptosis-sensitive and apoptosis-resistant cells. Specifically, the invention relates that apoptosis was induced in human cervix **carcinoma** cell line HeLa S3 by Fas activation. After the selection procedure, only a low number of living cells were present,. . . used as targets in diagnosis, therapeutics and drug screening, particularly for disorders associated with dysfunction of apoptotic processes, such as **tumors**.

IT Apoptosis
(anti-; method for identifying nucleic acid mols. (genes/cDNAs) associated with desired phenotype, including **cancer** cell properties, such as growth factor independence, induction of angiogenesis, anti-apoptosis, and evasion of immunity)

IT **Neoplasm**
(cells of, properties of; method for identifying nucleic acid mols. associated with desired phenotype, such as **cancer** cell properties, method involves mutagenesis (caused by irradiation or chemical mutagenesis) and/or genome rearrangements)

IT **Neoplasm**
(metastasis; method for identifying nucleic acid mols. (genes/cDNAs) associated with desired phenotype, including **cancer** cell properties, such as invasiveness, metastasis, loss of contact inhibition and extracellular matrix requirement)

IT Angiogenesis
Immunity
(method for identifying nucleic acid mols. (genes/cDNAs) associated with desired phenotype, including **cancer** cell properties, such as growth factor independence, induction of angiogenesis, anti-apoptosis, and evasion of immunity)

IT **Tumor** markers
(method for identifying nucleic acid mols. (genes/cDNAs) associated with desired phenotype, including **cancer** cell properties, such as growth factor independence, induction of angiogenesis, anti-apoptosis, and increase in levels of **tumor** markers)

IT Growth factors, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method for identifying nucleic acid mols. (genes/cDNAs) associated with desired phenotype, including **cancer** cell properties, such as growth factor independence, induction of angiogenesis, anti-apoptosis, increase in levels of **tumor** markers)

IT Extracellular matrix
(method for identifying nucleic acid mols. (genes/cDNAs) associated with desired phenotype, including **cancer** cell properties, such as invasiveness, metastasis, loss of contact inhibition and extracellular matrix requirement)

IT Genome
Mutagenesis
Radiation

(method for identifying nucleic acid mols. (genes/cDNAs) associated with desired phenotype, method involves mutagenesis (caused by irradiation or chemical mutagenesis) and/or genome rearrangements)

IT 9001-41-6, Neuroleukin 9001-50-7, Glyceraldehyde-3-phosphate dehydrogenase 9026-43-1, Serine/threonine protein kinase 52660-18-1, Protein kinase ck1 86102-31-0, TIMP 87397-91-9, Thymosin β10 90698-26-3, Ribosomal p70 S6 protein kinase 102925-39-3, β-Adrenergic receptor kinase 124861-55-8, TIMP-2 proteinase inhibitor 127464-60-2, Vascular endothelial growth factor 137632-06-5, Csk tyrosine kinase 137632-07-6, ERK1 protein kinase 140208-22-6, Cdc25B phosphatase 141467-20-1, Wee1 kinase 141760-45-4, Furin 143375-65-9, Cdc2 kinase 144713-50-8, ERK3 protein kinase 145539-86-2, HCK Tyrosine kinase 146279-87-0 146838-20-2, Gene bcr protein kinase 146838-30-4, MAPKAP kinase-2 147302-47-4, Gene trkC protein tyrosine kinase 148640-14-6, RAC protein kinase 149433-91-0, EphA2 receptor tyrosine kinase 150027-19-3, A-Raf-1 kinase 151662-26-9, Tyrosine kinase itk 152478-57-4, JAK2 protein kinase 152743-99-2, **ErbB** -4 receptor **tyrosine kinase** 152787-71-8, Protein kinase TTK 153190-46-6, Protein kinase MLK3 153190-61-5, Tyk2 kinase 154907-65-0, Checkpoint kinase Chk1 154907-68-3, Rse protein tyrosine kinase 156621-09-9, MSK1 protein kinase 156859-16-4, Gene ryk protein kinase 158129-99-8, GRK6 receptor kinase 163441-58-5, Hyl tyrosine kinase 165245-99-8, Protein kinase Plk1 169150-71-4, DAP kinase 170347-50-9, FAST kinase 170780-46-8, Protein tyrosine kinase PYK2 172306-41-1, Protein kinase PCTAIRE-1 172306-53-5, Protein kinase LIMK-1 172308-17-7, Matrix metalloproteinase-15 173585-04-1, Integrin-linked kinase 174206-56-5, Gene mnb protein kinase 175780-17-3, MAPKAP kinase 3 176023-60-2, Gene AKT2 protein kinase 176023-62-4, Protein kinase PKN 178037-70-2, Protein kinase SGK 179466-45-6, Protein kinase Ndr 182238-33-1, Gene RON receptor kinase 182372-11-8, Metalloproteinase ADAM12 184049-62-5, Protein phosphatase PYST1 187042-29-1, Cyclin G-associated kinase 188265-45-4, Gene KHS protein kinase 192230-91-4, MAPK kinase 3 193099-10-4, Metalloprotease ADAM15 194739-73-6, MAP kinase kinase 6 195740-69-3, Protein kinase ARK2 197664-51-0, Gene lok protein kinase 198228-69-2, Jun N-terminal kinase kinase 2 200578-48-9, Protein kinase IRAK-2 202420-94-8, Cdc25C-associated protein kinase 203945-19-1, Protein kinase BUB1 204784-44-1, Protein kinase SRPK2 204934-34-9, EphB3 receptor tyrosine kinase 216974-70-8, EphB4 receptor tyrosine kinase 219575-48-1, Ste20-like kinase 233284-43-0, Gene NEK3 protein kinase 252351-00-1, Metalloprotease ADAM-8 253170-37-5, MSK2 kinase 262450-51-1, Protein kinase MST3 268742-11-6, Protein kinase CHED 300830-60-8, Protein tyrosine phosphatase MEG2 300853-81-0, Protein tyrosine phosphatase ζ 300855-77-0, Protein tyrosine phosphatase 1C 301167-76-0, Protein tyrosine phosphatase CAAX2 303027-49-8, RPTP-μ 327046-95-7, MAP kinase kinase 5 329767-79-5, Protein tyrosine phosphatase σ 335605-46-4, MKK7 protein kinase 352521-00-7, Protein tyrosine phosphatase PRL-3 361186-44-9, Protein phosphatase PP5 362516-16-3, IKKα kinase 366806-33-9, CASEIN KINASE II 408328-74-5, IKKγ kinase 409105-92-6, Protein kinase MAST205 420790-04-1, Pim-2 protein kinase 444993-55-9, Gene VRK1 protein kinase (phosphorylating)

RL: ANT (Analyte); BSU (Biological study, unclassified); DGN (Diagnostic use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)

(identification of proteins (**kinases**, phosphatases, enzymes, and receptors) with enhanced expression in apoptosis-resistant cell clones, and their use in diagnosis, therapeutics and drug screening)

L8 ANSWER 19 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AB The invention relates to a combination therapy for the treatment of **tumors** and **tumor** metastases comprising administration of receptor **tyrosine kinase** antagonists/inhibitors, especially **ErbB** receptor antagonists, more preferably EGF receptor (Her 1) antagonists and anti-angiogenic agents, preferably integrin antagonists, optionally together with agents or therapy forms that have additive or synergistic efficacy when administered together with said combination of antagonists/inhibitors, such as chemotherapeutic agents and or **radiation** therapy. The therapy can result in a synergistic potential increase of the inhibition effect of each individual therapeutic on **tumor** cell proliferation, yielding more effective treatment than found by administering an individual component alone.

ACCESSION NUMBER: 2002:539555 HCAPLUS
DOCUMENT NUMBER: 137:108304
TITLE: Pharmaceutical compositions comprising Receptor tyrosine kinase-inhibiting antibodies and angiogenesis inhibitors for treating **cancer** and metastasis
INVENTOR(S): Goodman, Simon; Kreysch, Hans-Georg
PATENT ASSIGNEE(S): Merck Patent Gmbh, Germany
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002055106	A2	20020718	WO 2001-EP15241	20011221 <--
WO 2002055106	A3	20030306		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1349574	A2	20031008	EP 2001-273120	20011221
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001016575	A	20040106	BR 2001-16575	20011221
JP 2004520344	T2	20040708	JP 2002-555839	20011221
US 2004052785	A1	20040318	US 2003-250783	20030709

PRIORITY APPLN. INFO.:

EP 2001-100507	A	20010109
WO 2001-EP15241	W	20011221

TI Pharmaceutical compositions comprising Receptor tyrosine kinase-inhibiting antibodies and angiogenesis inhibitors for treating **cancer** and metastasis

PI WO 2002055106 A2 **20020718**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI WO 2002055106 A2 20020718 WO 2001-EP15241 20011221 <--
WO 2002055106 A3 20030306
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
EP 1349574 A2 20031008 EP 2001-273120 20011221
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
BR 2001016575 A 20040106 BR 2001-16575 20011221
JP 2004520344 T2 20040708 JP 2002-555839 20011221
US 2004052785 A1 20040318 US 2003-250783 20030709

AB The invention relates to a combination therapy for the treatment of **tumors** and **tumor** metastases comprising administration of receptor **tyrosine kinase** antagonists/inhibitors, especially **ErbB** receptor antagonists, more preferably EGF receptor (Her 1) antagonists and anti-angiogenic agents, preferably integrin antagonists, optionally together with agents or. . . that have additive or synergistic efficacy when administered together with said combination of antagonists/inhibitors, such as chemotherapeutic agents and or **radiation** therapy. The therapy can result in a synergistic potential increase of the inhibition effect of each individual therapeutic on **tumor** cell proliferation, yielding more effective treatment than found by administering an individual component alone.

ST receptor tyrosine kinase antibody integrin inhibitor **cancer** therapy; angiogenesis inhibitor EGFR VEGFR antibody metastasis therapy; chemotherapy radiotherapy EGFR antibody integrin antagonist **cancer** therapy

IT Receptors
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(angiogenesis; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Angiogenic factors
Growth inhibitors, animal
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(angiogenic growth-inhibiting factor; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Tyrosine kinase receptors
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antagonists or antibody inhibitor; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Epidermal growth factor receptors
Vascular endothelial growth factor receptors
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antagonists; pharmaceutical compns. comprising antibodies against

receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Drug delivery systems
(carriers; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Peptides, biological studies
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclic; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Antibodies and Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fragments; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Antibodies and Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fusion products; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Antibodies and Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(humanized; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Drug delivery systems
(immunoconjugates; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Integrins
neu (receptor)
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Jaw
(maxilla, superior; squamous cell **carcinoma**; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT **Neoplasm**
(metastasis, inhibitor; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Antibodies and Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Molecules
(non-immunol.; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Hormone receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(nuclear; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Angiogenesis inhibitors
Antitumor agents
Cytotoxic agents
Drug delivery systems
Epitopes
(pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Cytokines
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Fusion proteins (chimeric proteins)
RGD peptides
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Antibodies and Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT **Carcinoma**
(squamous cell; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Integrins
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(αvβ3, inhibitors; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Integrins
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(αvβ5, inhibitors; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT Integrins
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(αvβ6, inhibitors; pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

IT 137632-09-8, **ErbB**-2 receptor **kinase**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors; pharmaceutical compns. comprising antibodies against receptor **tyrosine kinase** and angiogenesis inhibitors for treating **cancer** and metastasis)

IT 3614-69-5, Fenistil 11056-06-7, Bleomycin 15663-27-1,

Cisplatin 23214-92-8, Doxorubicin 33069-62-4, **Paclitaxel** 66357-59-3, Zantac 95058-81-4, **Gemcitabine** 114977-28-5, **Docetaxel** 188968-51-6, Cilengitide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. comprising antibodies against receptor tyrosine kinase and angiogenesis inhibitors for treating **cancer** and metastasis)

L8 ANSWER 20 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AB The invention provides methods and compns. for inhibiting the activity of erbB-2. The methods and compns. are particularly useful for inhibiting cellular proliferative disorders, e.g. **cancer**, characterized by over-activity and/or inappropriate activity of erbB-2. More particularly, a method for the treatment of a cellular proliferative disorder characterized by over-activity or inappropriate activity of erbB-2 includes administering a therapeutically effective amount of soluble extract of houttuynum, or a compound selected from the group consisting of houttuyninum, Houttuymia cordata, neo-houttuyninum (decanoyl acetaldehyde), analogs thereof, pharmaceutically acceptable salts thereof, and/or prodrugs thereof.

ACCESSION NUMBER: 2002:408470 HCAPLUS
DOCUMENT NUMBER: 136:395950
TITLE: Houttuyninum compositions and methods for inhibiting the activity of erbB-2
INVENTOR(S): Yang, Dajun; Zhu, Xiao F.; Wang, Jingson; Zeng, Yixing
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002041828	A2	20020530	WO 2001-US43123	20011119 <--
WO 2002041828	A3	20020801		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002039258	A5	20020603	AU 2002-39258		20011119 <--
PRIORITY APPLN. INFO.:			US 2000-249272P	P	20001117
			WO 2001-US43123	W	20011119

PI WO 2002041828 A2 **20020530**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002041828	A2	20020530	WO 2001-US43123	20011119 <--
WO 2002041828	A3	20020801		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002039258 A5 20020603 AU 2002-39258 20011119 <--

AB . . . compns. for inhibiting the activity of erbB-2. The methods and compns. are particularly useful for inhibiting cellular proliferative disorders, e.g. **cancer**, characterized by over-activity and/or inappropriate activity of erbB-2. More particularly, a method for the treatment of a cellular proliferative disorder. . .

IT Antitumor agents
(bladder **carcinoma**; houttuyninum compns. and methods for inhibiting the activity of erbB-2)

IT Bladder
(**carcinoma**, inhibitors; houttuyninum compns. and methods for inhibiting the activity of erbB-2)

IT Antitumor agents
(cervix **carcinoma**; houttuyninum compns. and methods for inhibiting the activity of erbB-2)

IT Uterus, **neoplasm**
(cervix, **carcinoma**, inhibitors; houttuyninum compns. and methods for inhibiting the activity of erbB-2)

IT Intestine, **neoplasm**
(colon, inhibitors; houttuyninum compns. and methods for inhibiting the activity of erbB-2)

IT Liver, **neoplasm**
(hepatoma, inhibitors; houttuyninum compns. and methods for inhibiting the activity of erbB-2)

IT Brain, **neoplasm**
Ovary, **neoplasm**
Pancreas, **neoplasm**
Skin, **neoplasm**
Stomach, **neoplasm**
(inhibitors; houttuyninum compns. and methods for inhibiting the activity of erbB-2)

IT Antitumor agents
(**leukemia**; houttuyninum compns. and methods for inhibiting the activity of erbB-2)

IT Antitumor agents
(lung non-small-cell **carcinoma**; houttuyninum compns. and methods for inhibiting the activity of erbB-2)

IT Antitumor agents
(**melanoma**; houttuyninum compns. and methods for inhibiting the activity of erbB-2)

IT Head
Mammary gland
Neck, anatomical
Prostate gland
(**neoplasm**, inhibitors; houttuyninum compns. and methods for inhibiting the activity of erbB-2)

IT Nerve, **neoplasm**
(neuroblastoma, inhibitors; houttuyninum compns. and methods for inhibiting the activity of erbB-2)

IT Lung, **neoplasm**
(non-small-cell **carcinoma**, inhibitors; houttuyninum compns.

and methods for inhibiting the activity of erbB-2)

IT 60-92-4, Cyclic AMP 79079-06-4, EGF receptor **tyrosine kinase** 137632-09-8, ErbB2 receptor **tyrosine kinase** 142243-02-5, MAP kinase 148640-14-6, Akt kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(houttuyninum compns. and methods for inhibiting the activity of **erbB**-2)

IT 303-45-7, Gossypol 303-45-7D, Gossypol, analogs 15663-27-1, **Cisplatin** 23214-92-8, Doxorubicin 33419-42-0, VP-16 56505-80-7, Decanoyl acetaldehyde 56505-80-7D, Decanoyl acetaldehyde, analogs 83766-73-8 83766-73-8D, analogs 112714-99-5 112714-99-5D, analogs 118019-64-0 118019-64-0D, analogs 180288-69-1, Herceptin 431878-36-3 431878-36-3D, analogs 431878-37-4 431878-37-4D, analogs 431878-38-5 431878-38-5D, analogs 431878-39-6 431878-39-6D, analogs 431878-40-9 431878-40-9D, analogs 431878-41-0 431878-41-0D, analogs 431878-42-1 431878-42-1D, analogs 431878-43-2 431878-43-2D, analogs 431878-44-3 431878-44-3D, analogs 431878-45-4 431878-45-4D, analogs
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(houttuyninum compns. and methods for inhibiting the activity of erbB-2)

L8 ANSWER 21 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AB Cyclooxygenase-2 (COX-2) seems to be involved in critical steps of **cancer** onset and progression. Abnormalities of epidermal growth factor receptor (EGFR) and Her-2/neu have been actively investigated in ovarian **cancer** and associated with unfavorable clin. outcome. The involvement of COX-2 in **ErbB** family pathways has been proposed. We investigated by immunohistochem. the expression of COX-2, EGFR, and Her-2/neu in a series of advanced primary ovarian **cancers**. The study included 76 consecutive stage IIIC-IV ovarian **cancer** patients with measurable disease after first surgery. Immunohistochem. was performed on paraffin-embedded sections with rabbit antiserum against COX-2, murine monoclonal antibody (MoAb) 300G9 against Her-2/neu, and monoclonal antibody 108 against EGFR. No association among COX-2, EGFR, and HER-2/neu was found. COX-2 positivity was found in a statistically significant higher percentage of unresponsive cases (80.0%) than in patients responding to chemotherapy (35.7%) (P = 0.0008). The association between COX-2 positivity and poor chance of response to treatment was retained in multivariate anal. In the subgroup of patients who underwent explorative laparotomy COX-2-pos. cases showed a shorter overall survival (P = 0.049). COX-2 could represent a possible new marker of sensitivity to platin-based chemotherapy in ovarian **cancer**. The lack of association of COX-2 with EGFR or Her-2/neu suggests that the ability of COX-2 to predict **tumor** sensitivity to chemotherapy is not dependent on EGFR or Her-2/neu status and could be independently associated with prognosis. In this context, the availability of agents able to specifically interfere with COX-2, Her-2/neu, or EGFR **tyrosine kinase** is of potential interest.

ACCESSION NUMBER: 2002:309549 HCAPLUS
DOCUMENT NUMBER: 137:245502
TITLE: Cyclooxygenase-2 (COX-2), Epidermal Growth Factor Receptor (EGFR), and Her-2/neu Expression in Ovarian **Cancer**
AUTHOR(S): Ferrandina, G.; Ranelletti, F. O.; Lauriola, L.; Fanfani, F.; Legge, F.; Mottolese, M.; Nicotra, M. R.; Natali, P. G.; Zakut, V. H.; Scambia, G.

CORPORATE SOURCE: Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, Rome, 00165, Italy
SOURCE: Gynecologic Oncology (**2002**), 85(2), 305-310
CODEN: GYNOA3; ISSN: 0090-8258
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Cyclooxygenase-2 (COX-2), Epidermal Growth Factor Receptor (EGFR), and Her-2/neu Expression in Ovarian **Cancer**

SO Gynecologic Oncology (**2002**), 85(2), 305-310
CODEN: GYNOA3; ISSN: 0090-8258

AB Cyclooxygenase-2 (COX-2) seems to be involved in critical steps of **cancer** onset and progression. Abnormalities of epidermal growth factor receptor (EGFR) and Her-2/neu have been actively investigated in ovarian **cancer** and associated with unfavorable clin. outcome. The involvement of COX-2 in **ErbB** family pathways has been proposed. We investigated by immunohistochem. the expression of COX-2, EGFR, and Her-2/neu in a series of advanced primary ovarian **cancers**. The study included 76 consecutive stage IIIC-IV ovarian **cancer** patients with measurable disease after first surgery. Immunohistochem. was performed on paraffin-embedded sections with rabbit antiserum against COX-2, murine monoclonal. . . shorter overall survival (P = 0.049). COX-2 could represent a possible new marker of sensitivity to platin-based chemotherapy in ovarian **cancer**. The lack of association of COX-2 with EGFR or Her-2/neu suggests that the ability of COX-2 to predict **tumor** sensitivity to chemotherapy is not dependent on EGFR or Her-2/neu status and could be independently associated with prognosis. In this context, the availability of agents able to specifically interfere with COX-2, Her-2/neu, or EGFR **tyrosine kinase** is of potential interest.

ST cyclooxygenase EGF receptor neu ovarian **cancer** chemosensitivity prognosis

IT Ovary, **neoplasm**
(**adenocarcinoma**; cyclooxygenase-2, EGF receptors and neu expressions in advanced primary ovarian **cancers** in relation to outcome)

IT Chemotherapy
Death
Drug resistance
Human
Ovary, **neoplasm**
Prognosis
Tumor markers
(cyclooxygenase-2, EGF receptors and neu expressions in advanced primary ovarian **cancers** in relation to outcome)

IT Epidermal growth factor receptors
neu (receptor)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cyclooxygenase-2, EGF receptors and neu expressions in advanced primary ovarian **cancers** in relation to outcome)

IT 329900-75-6, Cyclooxygenase-2
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase-2, EGF receptors and neu expressions in advanced primary ovarian **cancers** in relation to outcome)

IT 15663-27-1, **Cisplatin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(cyclooxygenase-2, EGF receptors and neu expressions in advanced primary ovarian **cancers** in relation to outcome)
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 22 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AB The paper was wrongly published as a "Review" article; the correct section heading for this paper is "Original Paper".
ACCESSION NUMBER: 2001:526833 HCAPLUS
DOCUMENT NUMBER: 138:217504
TITLE: The relative role of ErbB1 - 4 receptor tyrosine kinases in **radiation** signal transduction responses of human **carcinoma** cells. [Erratum to document cited in CA135:16133]]
AUTHOR(S): Bowers, G.; Reardon, D.; Hewitt, T.; Dent, P.; Mikkelsen, R. B.; Valerie, K.; Lammering, G.; Amir, C.; Schmidt-Ullrich, R. K.
CORPORATE SOURCE: Department of Radiation Oncology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, 23298-0058, USA
SOURCE: Oncogene (**2001**), 20(29), 3927
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
TI The relative role of ErbB1 - 4 receptor tyrosine kinases in **radiation** signal transduction responses of human **carcinoma** cells. [Erratum to document cited in CA135:16133]]
SO Oncogene (**2001**), 20(29), 3927
CODEN: ONCNES; ISSN: 0950-9232
ST erratum **ErbB** receptor **tyrosine kinase** signal transduction MAPK **radiation**; **ErbB** receptor **tyrosine kinase** signal transduction MAPK **radiation** erratum; receptor **tyrosine kinase** signal transduction MAPK **radiation carcinoma** erratum
IT **Carcinoma**
Human
Radiotherapy
Signal transduction, biological
(**ErbB** receptor **tyrosine kinases** role in signal transduction response to **radiation** in human **carcinoma** (Erratum))
IT Epidermal growth factor receptors
neu (receptor)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**ErbB** receptor **tyrosine kinases** role in signal transduction response to **radiation** in human **carcinoma** (Erratum))
IT Growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**erbB**-3; **ErbB** receptor **tyrosine kinases** role in signal transduction response to **radiation** in human **carcinoma** (Erratum))
IT Growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(heregulin, **ErbB**-4; **ErbB** receptor **tyrosine kinases** role in signal transduction response to

radiation in human **carcinoma** (Erratum))
IT 79079-06-4, **ErbB** receptor **tyrosine kinase**
142805-58-1, MAPK **kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**ErbB** receptor **tyrosine kinases** role in
signal transduction response to **radiation** in human
carcinoma (Erratum))

L8 ANSWER 23 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AB Activation of the epidermal growth receptor (ErbB1) occurs within minutes of a **radiation** exposure. Immediate downstream consequences of this activation are currently indistinguishable from those obtained with growth factors (GF), e.g. stimulation of the pro-proliferative mitogen-activated protein kinase (MAPK). To identify potential differences, the effects of GFs and **radiation** on other members of the ErbB family have been compared in mammary **carcinoma** cell lines differing in their ErbB expression profiles. Treatment of cells with EGF (ErbB1-specific) or heregulin (ErbB4-specific) resulted in a hierarchic transactivations of ErbB2 and ErbB3 dependent on GF binding specificity. In contrast, **radiation** indiscriminately activated all ErbB species with the activation profile reflecting that cell ErbB expression profile. Downstream consequences of these ErbB interactions were examined with MAPK after specifically inhibiting ErbB1 (or 4) with tyrphostin AG1478 or ErbB2 with tyrphostin AG825. MAPK activation by GFs or **radiation** was completely inhibited by AG1478 indicating total dependence on ErbB1 (or 4) depending on which ErbB is expressed. Inhibiting ErbB2 caused an enhanced MAPK response simulating an amplified ErbB1 (or 4) response. Thus ErbB2 is a modulator of ErbB1 (or 4) function leading to different MAPK response profiles to GF or **radiation** exposure.

ACCESSION NUMBER: 2001:251306 HCAPLUS
DOCUMENT NUMBER: 135:16133
TITLE: The relative role of ErbB1-4 receptor tyrosine kinases in **radiation** signal transduction responses of human **carcinoma** cells
AUTHOR(S): Bowers, G.; Reardon, D.; Hewitt, T.; Dent, P.; Mikkelsen, R. B.; Valerie, K.; Lammering, G.; Amir, C.; Schmidt-Ullrich, R. K.
CORPORATE SOURCE: Department of Radiation Oncology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, 23298-0058, USA
SOURCE: Oncogene (**2001**), 20(11), 1388-1397
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

TI The relative role of ErbB1-4 receptor tyrosine kinases in **radiation** signal transduction responses of human **carcinoma** cells
SO Oncogene (**2001**), 20(11), 1388-1397
CODEN: ONCNES; ISSN: 0950-9232
AB Activation of the epidermal growth receptor (ErbB1) occurs within minutes of a **radiation** exposure. Immediate downstream consequences of this activation are currently indistinguishable from those obtained with growth factors (GF), e.g. stimulation of the pro-proliferative mitogen-activated protein kinase (MAPK). To identify potential differences, the effects of GFs and **radiation** on other members

of the ErbB family have been compared in mammary **carcinoma** cell lines differing in their ErbB expression profiles. Treatment of cells with EGF (ErbB1-specific) or heregulin (ErbB4-specific) resulted in a hierarchic transactivations of ErbB2 and ErbB3 dependent on GF binding specificity. In contrast, **radiation** indiscriminately activated all ErbB species with the activation profile reflecting that cell ErbB expression profile. Downstream consequences of these ErbB. . . MAPK after specifically inhibiting ErbB1 (or 4) with tyrphostin AG1478 or ErbB2 with tyrphostin AG825. MAPK activation by GFs or **radiation** was completely inhibited by AG1478 indicating total dependence on ErbB1 (or 4) depending on which ErbB is expressed. Inhibiting ErbB2. . . response. Thus ErbB2 is a modulator of ErbB1 (or 4) function leading to different MAPK response profiles to GF or **radiation** exposure.

ST **ErbB** receptor **tyrosine kinase** signal transduction MAPK **radiation carcinoma**

IT **Carcinoma**
Radiotherapy
Signal transduction, biological
(**ErbB** receptor **tyrosine kinases** role in signal transduction response to **radiation** in human **carcinoma**)

IT Epidermal growth factor receptors
neu (receptor)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**ErbB** receptor **tyrosine kinases** role in signal transduction response to **radiation** in human **carcinoma**)

IT Growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**erbB**-3; **ErbB** receptor **tyrosine kinases** role in signal transduction response to **radiation** in human **carcinoma**)

IT Growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(heregulin, **ErbB**-4; **ErbB** receptor **tyrosine kinases** role in signal transduction response to **radiation** in human **carcinoma**)

IT 142805-58-1, MAPK **kinase**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**ErbB** receptor **tyrosine kinases** role in signal transduction response to **radiation** in human **carcinoma**)

IT 79079-06-4, **ErbB** receptor **tyrosine kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**ErbB** receptor **tyrosine kinases** role in signal transduction response to **radiation** in human **carcinoma**)

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 24 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AB The authors disclose the treatment of disorders characterized by the overexpression of ErbB2. More specifically, human patients are treated with a combination of an anti-ErbB2 antibody and a chemotherapeutic agent other than an anthracycline (e.g., doxorubicin or epirubicin). Preferably, the chemotherapeutic agent is Taxol.

ACCESSION NUMBER: 1999:405000 HCAPLUS
DOCUMENT NUMBER: 131:43391
TITLE: Combination therapy of **cancer** with anti-ErbB2 antibodies
INVENTOR(S): Shak, Steven; Paton, Virginia E.
PATENT ASSIGNEE(S): Genentech, Inc., USA
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9931140	A1	19990624	WO 1998-US26266	19981210 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
ZA 9811162	A	20000607	ZA 1998-11162	19981207 <--
CA 2311409	AA	19990624	CA 1998-2311409	19981210 <--
AU 9919081	A1	19990705	AU 1999-19081	19981210 <--
EP 1037926	A1	20000927	EP 1998-963840	19981210 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200001689	T2	20010122	TR 2000-200001689	19981210 <--
BR 9815363	A	20011016	BR 1998-15363	19981210 <--
JP 2002508397	T2	20020319	JP 2000-539062	19981210 <--
NZ 504597	A	20030530	NZ 2000-504597	20000517
NO 2000002957	A	20000811	NO 2000-2957	20000609 <--
US 2003147884	A1	20030807	US 2003-356824	20030203
US 2004037823	A9	20040226		
US 2003170234	A1	20030911	US 2003-406925	20030404

PRIORITY APPLN. INFO.:

US 1997-69346P	P	19971212
US 1998-208649	A3	19981210
US 1998-209023	A3	19981210
WO 1998-US26266	W	19981210

TI Combination therapy of **cancer** with anti-ErbB2 antibodies
PI WO 9931140 A1 **19990624**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9931140	A1	19990624	WO 1998-US26266	19981210 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG,				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
ZA 9811162	A	20000607	ZA 1998-11162	
CA 2311409	AA	19990624	CA 1998-23114	

DELACROIX

AU 9919081	A1	19990705	AU 1999-19081	19981210 <--
EP 1037926	A1	20000927	EP 1998-963840	19981210 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200001689	T2	20010122	TR 2000-200001689	19981210 <--
BR 9815363	A	20011016	BR 1998-15363	19981210 <--
JP 2002508397	T2	20020319	JP 2000-539062	19981210 <--
NZ 504597	A	20030530	NZ 2000-504597	20000517
NO 2000002957	A	20000811	NO 2000-2957	20000609 <--
US 2003147884	A1	20030807	US 2003-356824	20030203
US 2004037823	A9	20040226		
US 2003170234	A1	20030911	US 2003-406925	20030404

ST ErbB2 receptor antibody **tumor** combination therapy

IT Antitumor agents
(bladder **carcinoma**; combination therapy of **cancer** with antibodies to erbB-2 receptor)

IT Bladder
Bladder
Lung, **neoplasm**
Lung, **neoplasm**
(**carcinoma**, inhibitors; combination therapy of **cancer** with antibodies to erbB-2 receptor)

IT Uterus, **neoplasm**
Uterus, **neoplasm**
(cervix, inhibitors; combination therapy of **cancer** with antibodies to erbB-2 receptor)

IT Antitumor agents
(cervix; combination therapy of **cancer** with antibodies to erbB-2 receptor)

IT Anthracyclines
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(chemotherapeutics; combination **cancer** therapy with anti-erbB-2 receptor antibodies where contraindication exists for)

IT Intestine, **neoplasm**
Intestine, **neoplasm**
(colon, inhibitors; combination therapy of **cancer** with antibodies to erbB-2 receptor)

IT Antitumor agents
(colon; combination therapy of **cancer** with antibodies to erbB-2 receptor)

IT Intestine, **neoplasm**
Intestine, **neoplasm**
(colorectal, inhibitors; combination therapy of **cancer** with antibodies to erbB-2 receptor)

IT Antitumor agents
(colorectal; combination therapy of **cancer** with antibodies to erbB-2 receptor)

IT neu (receptor)
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(combination therapy of **cancer** with antibodies to)

IT Antitumor agents
(combination therapy of **cancer** with antibodies to erbB-2 receptor)

IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy of **cancer** with antibodies to erbB-2 receptor)

IT Antitumor agents
(digestive tract; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Antitumor agents
(endometrium **carcinoma**; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Uterus, **neoplasm**
Uterus, **neoplasm**
(endometrium, **carcinoma**, inhibitors; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Neuroglia
Neuroglia
(glioblastoma, inhibitors; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Antitumor agents
(glioblastoma; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Antitumor agents
(head; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Liver, **neoplasm**
Liver, **neoplasm**
(hepatoma, inhibitors; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Antitumor agents
(hepatoma; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(humanized; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Taxanes
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination **cancer** therapy with anti-erbB-2 receptor antibodies)
IT Kidney, **neoplasm**
Kidney, **neoplasm**
Ovary, **neoplasm**
Ovary, **neoplasm**
Pancreas, **neoplasm**
Pancreas, **neoplasm**
Thyroid gland, **neoplasm**
Thyroid gland, **neoplasm**
(inhibitors; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Antitumor agents
Antitumor agents
(kidney; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Antitumor agents
(lung **carcinoma**; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Antitumor agents
(lung small-cell **carcinoma**; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Antitumor agents
(mammary gland; combination therapy of **cancer** with antibodies

to erbB-2 receptor)
IT Antitumor agents
(neck; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Digestive tract
Digestive tract
Head
Head
Mammary gland
Mammary gland
Neck, anatomical
Neck, anatomical
Prostate gland
Prostate gland
Salivary gland
(**neoplasm**, inhibitors; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Epitopes
(of erbB-2 receptor for antibodies in combination **cancer** therapy)
IT Antitumor agents
Antitumor agents
(ovary; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Antitumor agents
Antitumor agents
(pancreas; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Antitumor agents
(prostate gland; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Lung, **neoplasm**
Lung, **neoplasm**
(small-cell **carcinoma**, inhibitors; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Antitumor agents
(squamous cell **carcinoma**; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Antitumor agents
Antitumor agents
(thyroid; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Reproductive organ
Reproductive tract
(vulva, **neoplasm**, inhibitors; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT Antitumor agents
(vulva; combination therapy of **cancer** with antibodies to erbB-2 receptor)
IT 180288-69-1, Herceptin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination **cancer** therapy with)
IT 137632-09-8, c-**ErbB**-2 **tyrosine kinase**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(combination therapy of **cancer** with antibodies to)
IT 33069-62-4, **Paclitaxel** 114977-28-5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(in combination **cancer** therapy with anti-erbB-2 receptor antibodies)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 25 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AB The present invention relates to methods for the inhibition, of the gene product of the neu oncogene, p185neu **tyrosine kinase**. Overexpression of the neu oncogene leads to chemoresistance. The methods disclosed involve the novel use of E1A and/or SV40 large T antigen in combination with chemotherapeutic drugs to treat **carcinoma**. Furthermore, E1A surprisingly potentiates the antineoplastic effects of the chemotherapeutic agents. The inventors propose that E1A sensitizes **cancer** cells such that they become amenable to treatment by chemotherapeutic drugs. The ability of the E1A gene to suppress neu gene expression, neu gene-mediated **tumorigenicity**, neu gene-mediated metastasis, and c-**erbB**/neu expression in human ovarian **carcinoma** was demonstrated. Addnl., the suppression of neu with large T antigen was shown.

ACCESSION NUMBER: 1997:640770 HCAPLUS
DOCUMENT NUMBER: 127:303327
TITLE: Sensitization with E1A or SV40 large T antigen of HER-2/neu-overexpressing **cancer** cells to chemotherapy
INVENTOR(S): Hung, Mien-Chie; Ueno, Naoto T.
PATENT ASSIGNEE(S): Board of Regents, the University of Texas System, USA; Hung, Mien-Chie; Ueno, Naoto T.
SOURCE: PCT Int. Appl., 210 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9735012	A1	19970925	WO 1997-US3830	19970319 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2250222	AA	19970925	CA 1997-2250222	19970319 <--
AU 9722055	A1	19971010	AU 1997-22055	19970319 <--
AU 733737	B2	20010524		
EP 894139	A1	19990203	EP 1997-914999	19970319 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001505529	T2	20010424	JP 1997-533534	19970319 <--
US 6395712	B1	20020528	US 1997-809021	19970319 <--
US 2004053863	A1	20040318	US 2001-943984	20010831

PRIORITY APPLN. INFO.:

US 1996-13750P	P	19960320
US 1997-809021	A1	19970319
WO 1997-US3830	W	19970319

TI Sensitization with E1A or SV40 large T antigen of HER-2/neu-overexpressing **cancer** cells to chemotherapy

PI WO 9735012 A1 **19970925**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9735012	A1	19970925	WO 1997-US3830	19970319 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2250222	AA	19970925	CA 1997-2250222	19970319 <--
AU 9722055	A1	19971010	AU 1997-22055	19970319 <--
AU 733737	B2	20010524		
EP 894139	A1	19990203	EP 1997-914999	19970319 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001505529	T2	20010424	JP 1997-533534	19970319 <--
US 6395712	B1	20020528	US 1997-809021	19970319 <--
US 2004053863	A1	20040318	US 2001-943984	20010831

AB The present invention relates to methods for the inhibition, of the gene product of the neu oncogene, p185neu **tyrosine kinase**. Overexpression of the neu oncogene leads to chemoresistance. The methods disclosed involve the novel use of E1A and/or SV40 large T antigen in combination with chemotherapeutic drugs to treat **carcinoma**. Furthermore, E1A surprisingly potentiates the antineoplastic effects of the chemotherapeutic agents. The inventors propose that E1A sensitizes **cancer** cells such that they become amenable to treatment by chemotherapeutic drugs. The ability of the E1A gene to suppress neu gene expression, neu gene-mediated **tumorigenicity**, neu gene-mediated metastasis, and c-**erbB**/neu expression in human ovarian **carcinoma** was demonstrated. Addnl., the suppression of neu with large T antigen was shown.

ST **tumor** chemotherapy E1A large T antigen; neu oncogene chemotherapy E1A T antigen

IT Gene, microbial
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(E1A; sensitization with E1A or SV40 large T antigen of HER-2/neu-overexpressing **cancer** cells to chemotherapy)

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(c-erbB2; sensitization with E1A or SV40 large T antigen of HER-2/neu-overexpressing **cancer** cells to chemotherapy)

IT Alkylating agents, biological
(chemotherapy with; sensitization with E1A or SV40 large T antigen of HER-2/neu-overexpressing **cancer** cells to chemotherapy)

IT Alkaloids, biological studies
Antibiotics
Tumor necrosis factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chemotherapy with; sensitization with E1A or SV40 large T antigen of HER-2/neu-overexpressing **cancer** cells to chemotherapy)

IT Transformation, **neoplastic**

(inhibition of; sensitization with E1A or SV40 large T antigen of HER-2/neu-overexpressing **cancer** cells to chemotherapy)

IT Lung, **neoplasm**
(inhibitors; sensitization with E1A or SV40 large T antigen of HER-2/neu-overexpressing **cancer** cells to chemotherapy)

IT Antigens
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(large T, gene for; sensitization with E1A or SV40 large T antigen of HER-2/neu-overexpressing **cancer** cells to chemotherapy)

IT Antitumor agents
(lung; sensitization with E1A or SV40 large T antigen of HER-2/neu-overexpressing **cancer** cells to chemotherapy)

IT Liposomes
Virus vectors
(neu-suppressing gene introduction with; sensitization with E1A or SV40 large T antigen of HER-2/neu-overexpressing **cancer** cells to chemotherapy)

IT Gene
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neu-suppressing; sensitization with E1A or SV40 large T antigen of HER-2/neu-overexpressing **cancer** cells to chemotherapy)

IT Antitumor agents
Chemotherapy
Neoplasm
(sensitization with E1A or SV40 large T antigen of HER-2/neu-overexpressing **cancer** cells to chemotherapy)

IT Human adenovirus
(vectors, neu-suppressing gene introduction with; sensitization with E1A or SV40 large T antigen of HER-2/neu-overexpressing **cancer** cells to chemotherapy)

IT 50-18-0, Cyclophosphamide 50-76-0, Dactinomycin 51-75-2, Mechlorethamine 52-24-4, Thiotepa 55-98-1, Busulfan 57-22-7, Vincristine 148-82-3, Melphalan 154-93-8, Carmustine 305-03-3 865-21-4, Vinblastine 1404-00-8, Mitomycin 3778-73-2, Ifosfamide 11056-06-7, Bleomycin 13010-47-4, Lomustine 15663-27-1, **Cisplatin** 18883-66-4, Streptozocin 20830-81-3, Daunorubicin 23214-92-8, Doxorubicin 33069-62-4, Taxol 33419-42-0, VP16 58957-92-9, Idarubicin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chemotherapy with; sensitization with E1A or SV40 large T antigen of HER-2/neu-overexpressing **cancer** cells to chemotherapy)

L8 ANSWER 26 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AB The exposure of mammalian cells to UR **radiation** (UV) may lead to DNA damage resulting in mutation and thus possibly **cancer**, while irradiation can further act as a potent **tumor** promoter. In addition UV induces p21ras-mediated signaling leading to activation of transcription factors such as AP-1 and NF-κB, as well as activation of the Src tyrosine kinase. This UV-response has been well studied in mammalian cells and furthermore is conserved in yeast, however the most upstream components of this signal transduction pathway have remained elusive. Here we show that UV rapidly activates both the EGF receptor and insulin receptor, as shown by tyrosine phosphorylation of these receptors. We demonstrate that this activation is due to autophosphorylation a sit only occurs in cells containing receptors with a functional kinase domain. We have

further analyzed the propagation of the UV-induced signal to downstream events such as, IRS-1 and Shc tyrosine phosphorylation, phosphatidylinositol 3-kinase activation, leukotriene synthesis, MAP kinase activation and gene induction all of which are activated by UV irradiation Importantly, we demonstrate that in cells expressing a "kinase-dead' receptor mutant the UV-response is inhibited, blocking leukotriene synthesis, MAP kinase activation and transcriptional induction. Furthermore, prior-stimulation of cells with UV appears to reduce further responsiveness to addition of growth factor suggesting a common signaling pathway. These data demonstrate a critical role for receptor-mediated events in regulating the response of mammalian cells to UV exposure.

ACCESSION NUMBER: 1995:758252 HCAPLUS
DOCUMENT NUMBER: 123:164145
TITLE: UV activation of receptor tyrosine kinase activity
AUTHOR(S): Coffer, Paul J.; Burgering, Boudewijn M. Th.; Peppelenbosch, Maikel P.; Bos, Johannes L.; Kruijer, Wiebe
CORPORATE SOURCE: Hubrecth Lab., Netherlands Inst. Developmental Biol., Utrecht, 3584, Neth.
SOURCE: Oncogene (**1995**), 11(3), 561-9
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Oncogene (**1995**), 11(3), 561-9
CODEN: ONCNES; ISSN: 0950-9232
AB The exposure of mammalian cells to UR **radiation** (UV) may lead to DNA damage resulting in mutation and thus possibly **cancer**, while irradiation can further act as a potent **tumor** promoter. In addition UV induces p21ras-mediated signaling leading to activation of transcription factors such as AP-1 and NF-κB, as well. . .
ST UV **radiation** receptor tyrosine kinase activation
IT Ultraviolet **radiation**
(UV activation of receptor tyrosine kinase activity)
IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(epidermal growth factor/α-transforming growth factor, gene c-**erbB**, UV activation of receptor **tyrosine kinase** activity)
IT Animal growth regulator receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(α-transforming growth factor gene c- **erbB**, UV activation of receptor **tyrosine kinase** activity)

L8 ANSWER 27 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AB Single-chain Fv mols. in monovalent (sFv) and divalent [(sFv')2] forms exhibit highly specific **tumor** targeting in mice as a result of their small size and rapid systemic clearance. As a consequence, there is a rapid reversal of the sFv blood/**tumor** gradient, resulting in diminished retention of sFv species in **tumors**. In this report we investigate two distinct strategies, dose escalation and repetitive i.v. dosing, aiming to increase the absolute selective retention of radiolabeled anti-c-erbB-2 125I-741F8 (sFv')2 in c-erbB-2-overexpressing SK-OV-3 **tumors** in mice with severe combined immunodeficiency

(SCID). A dose-escalation strategy was applied to single i.v. injections of 125I-741F8 (sFv')2. Doses from 50 μg to 1000 μg were administered without a significant decrease in **tumor** targeting or specificity. High doses resulted in large increases in the absolute retention of 125I-741F8 (sFv')2. For example, raising the administered dose from 50 μg to 1000 μg increased the **tumor** retention 24 h after injection from 0.46 μg/g to 9.5 μg/g, and resulted in a net increase of greater than 9 μg/g. Over the same dose range, the liver retention rose from 0.06 μg/g to 1 μg/g, and resulted in a net increase of less than 1 μg/g. The retention of 9.5 μg/g in **tumor** 24 h following the 1000-μg dose of (sFv')2 was comparable to that seen 24 h after a 50-μg dose of 125I-741F8 IgG, indicating that the use of large doses of (sFv')2 may partially offset their rapid clearance. When two doses were administered by i.v. injection 24 h apart, the specificity of delivery to **tumor** observed after the first dose was maintained following the second injection. **Tumor** retention of 125I-741F8 (sFv')2 was 0.32 μg/g at 24 h and 0.22 μg/g at 48 h following a single injection of 20 μg, while 0.04 μg/mL and 0.03 μg/mL were retained in blood at the same assay times. After a second 20-μg injection at the 24-h assay time, **tumor** retention increased to 0.49 μg/g, and blood retention was 0.06 μg/mL, at the 48-h point. These results suggest that multiple high-dose administrations of radiolabeled 741F8 (sFv')2 may lead to the selective **tumor** localization of therapeutic **radiation** doses.

ACCESSION NUMBER: 1995:754660 HCAPLUS
DOCUMENT NUMBER: 123:250143
TITLE: Optimization of in vivo **tumor** targeting in SCID mice with divalent forms of 741F8 anti-c-erbB-2 single-chain Fv: effects of dose escalation and repeated IV administration
AUTHOR(S): Adams, Gregory P.; McCartney, John E.; Wolf, Ellen J.; Eisenberg, Jamie; Tai, Mei-Sheng; Huston, James S.; Stafford, Walter F., III; Bookman, Michael A.; Houston, L. L.; Weiner, Louis M.
CORPORATE SOURCE: Dep. Med. Oncol., Fox Chase Cancer Cent., Philadelphia, PA, 19111, USA
SOURCE: Cancer Immunology Immunotherapy (**1995**), 40(5), 299-306
CODEN: CIIMDN; ISSN: 0340-7004
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Optimization of in vivo **tumor** targeting in SCID mice with divalent forms of 741F8 anti-c-erbB-2 single-chain Fv: effects of dose escalation and repeated IV administration
SO Cancer Immunology Immunotherapy (**1995**), 40(5), 299-306
CODEN: CIIMDN; ISSN: 0340-7004
AB Single-chain Fv mols. in monovalent (sFv) and divalent [(sFv')2] forms exhibit highly specific **tumor** targeting in mice as a result of their small size and rapid systemic clearance. As a consequence, there is a rapid reversal of the sFv blood/**tumor** gradient, resulting in diminished retention of sFv species in **tumors**. In this report we investigate two distinct strategies, dose escalation and repetitive i.v. dosing, aiming to increase the absolute selective retention of radiolabeled anti-c-erbB-2 125I-741F8 (sFv')2 in c-erbB-2-overexpressing SK-OV-3 **tumors** in mice with severe combined immunodeficiency (SCID). A dose-escalation strategy was applied to single i.v. injections

of 125I-741F8 (sFv')2. Doses from 50 μg to 1000 μg were administered without a significant decrease in **tumor** targeting or specificity. High doses resulted in large increases in the absolute retention of 125I-741F8 (sFv')2. For example, raising the administered dose from 50 μg to 1000 μg increased the **tumor** retention 24 h after injection from 0.46 μg/g to 9.5 μg/g, and resulted in a net increase of greater than. . . to 1 μg/g, and resulted in a net increase of less than 1 μg/g. The retention of 9.5 μg/g in **tumor** 24 h following the 1000-μg dose of (sFv')2 was comparable to that seen 24 h after a 50-μg dose of. . . offset their rapid clearance. When two doses were administered by i.v. injection 24 h apart, the specificity of delivery to **tumor** observed after the first dose was maintained following the second injection. **Tumor** retention of 125I-741F8 (sFv')2 was 0.32 μg/g at 24 h and 0.22 μg/g at 48 h following a single injection. . . μg/mL were retained in blood at the same assay times. After a second 20-μg injection at the 24-h assay time, **tumor** retention increased to 0.49 μg/g, and blood retention was 0.06 μg/mL, at the 48-h point. These results suggest that multiple high-dose administrations of radiolabeled 741F8 (sFv')2 may lead to the selective **tumor** localization of therapeutic **radiation** doses.

ST **tumor** targeting cerbB2 protein antibody Fv; radioantibody Fv **tumor** targeting cerbB2 protein

IT **Neoplasm**
(effects of repeated administration and dosage on **tumor** targeting with divalent forms of 741F8 anti-c-erbB-2 single-chain Fv radiolabeled antibody)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(effects of repeated administration and dosage on **tumor** targeting with divalent forms of 741F8 anti-c-erbB-2 single-chain Fv radiolabeled antibody)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p185c-erbB2, effects of repeated administration and dosage on **tumor** targeting with divalent forms of 741F8 anti-c-erbB-2 single-chain Fv radiolabeled antibody)

IT 14158-31-7DP, conjugates with Fv fragment, biological studies
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(effects of repeated administration and dosage on **tumor** targeting with divalent forms of 741F8 anti-c-erbB-2 single-chain Fv radiolabeled antibody)

IT 137632-09-8, c-**ErbB**-2 **tyrosine kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(effects of repeated administration and dosage on **tumor** targeting with divalent forms of 741F8 anti-c-**erbB**-2 single-chain Fv radiolabeled antibody)

FILE 'MEDLINE' ENTERED AT 22:03:15 ON 17 SEP 2004

FILE 'HCAPLUS' ENTERED AT 22:03:15 ON 17 SEP 2004
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(FILE 'HOME' ENTERED AT 22:01:34 ON 17 SEP 2004)

FILE 'REGISTRY' ENTERED AT 22:01:44 ON 17 SEP 2004
E CI-1033/CN
E CI 1033/CN
L1 1 S E3

FILE 'MEDLINE, HCAPLUS' ENTERED AT 22:03:15 ON 17 SEP 2004

=> s l1 and erbB(p)tyrosin?(p)kinas?
L2 10 L1 AND ERBB(P) TYROSIN?(P) KINAS?

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3 8 DUP REM L2 (2 DUPLICATES REMOVED)

=> d l3 abs cbib kwic hitrn 1-8

L3 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
AB Methods are provided for treating diseases associated with abnormal activity of kinases. The method comprises: administering a DNA methylation inhibitor to the patient in therapeutically effective amount; and administering a kinase inhibitor to the patient in therapeutically effective amount, such that the in vivo activity of the kinase is reduced relative to that prior to the treatment. The method can be used to treat cancer associated with abnormal activity of kinases such as phosphatidylinositol 3'-kinase (PI3K), protein kinases including serine/threonine kinases such as Raf kinases, protein kinase kinases such as MEK, and tyrosine kinases such as those in the epidermal growth factor receptor family (EGFR), platelet-derived growth factor receptor family (PDGFR), vascular endothelial growth factor receptor (VEGFR) family, nerve growth factor receptor family (NGFR), fibroblast growth factor receptor family (FGFR) insulin receptor family, ephrin receptor family, Met family, Ror family, c-kit family, Src family, Fes family, JAK family, Fak family, Btk family, Syk/ZAP-70 family, and Abl family.
2004:533967 Document Number 141:65147 Method for treating diseases associated with abnormal tyrosine kinase activity by administering a DNA methylation inhibitor and a tyrosine kinase inhibitor. Lyons, John; Rubinfeld, Joseph (USA). U.S. Pat. Appl. Publ. US 2004127453 A1 20040701, 19 pp., Cont.-in-part of U.S. Ser. Number -71,849. (English). CODEN: USXXCO. APPLICATION: US 2002-206854 20020726. PRIORITY: US 2002-71849 20020207.
IT Growth factor receptors
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(**erbB**-3, inhibitors; treating diseases associated with abnormal **tyrosine kinase** activity by administering DNA methylation inhibitors and **tyrosine kinase** inhibitors)
IT 180288-69-1, Herceptin 184475-35-2, Iressa 194423-15-9, PD168393

DELACROIX

205923-56-4, IMC-C225 257933-82-7, EKB-569 **289499-45-2**, CI1033
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as EGFR tyrosine kinase inhibitor; treating diseases associated with abnormal tyrosine kinase activity by administering DNA methylation inhibitors and tyrosine kinase inhibitors)

IT **289499-45-2**, CI1033
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as EGFR tyrosine kinase inhibitor; treating diseases associated with abnormal tyrosine kinase activity by administering DNA methylation inhibitors and tyrosine kinase inhibitors)

L3 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AB A review. Lung cancer is the leading cause of death worldwide. Current treatment modalities, including chemotherapy, radiotherapy and surgery, provide only limited improvement in the natural course of this disease. Therefore, the development of new therapeutic strategies is highly awaited. This review focuses on recent achievements on a novel class of anticancer drugs targeting the EGFR (Epidermal Growth Factor Receptor). The EGFR family is a group of four structurally similar growth factor receptors with **tyrosine-kinase** activity (EGFR, HER2/neu, **ErbB**-3, **ErbB**-4), which dimerize upon binding with a number of ligands, including EGF (Epidermal Growth Factor) and TGF (Transforming Growth Factor), allowing downstream transduction of mitogenic signals. Overexpression of EGFR and HER2 is frequently found in non-small-cell lung cancer (NSCLC), which accounts for over 80% of all malignant lung tumors, and has been associated with a worse clin. outcome. New agents developed to inhibit EGFR function include monoclonal antibodies and small-mol. receptor **tyrosine-kinase** inhibitors. In this review, results of most recent clin. with EGFR inhibitors including monoclonal antibodies, such as Trastuzumab (Herceptin), IMC-C225 (Cetuximab) and others (ABX-EGF, EMD 72000), and **tyrosine-kinase** inhibitors, such as ZD1839 (Gefitinib, Iressa), OSI-774 (Erlotinib, Tarceva) and others (CI-1033, GW2016), are summarized. In particular, final results of phase II (IDEAL 1 and 2) and III (INTACT 1 and 2) studies of ZD1839 are reported. In IDEAL trials (ZD1839 single agent in patients pre-treated with chemotherapy) there was clear evidence of tumor regression, symptoms improvement and overall clin. benefit, whereas in the two INTACT trials (ZD1839 in combination with standard platinum-based chemotherapy in chemo-naive patients) ZD1839 did not improve either survival or other clin. endpoints. Possible explanations for these contradictory results and future perspectives are discussed.

2004:280687 Document Number 140:296746 Epidermal growth factor receptor inhibitors: a new prospective in the treatment of lung cancer. Tiseo, M.; Loprevite, M.; Ardizzoni, A. (Division of Medical Oncology A Istituto Nazionale per la Ricerca sul Cancro Genova, Genoa, 16132, Italy). Current Medicinal Chemistry: Anti-Cancer Agents, 4(2), 139-148 (English) 2004. CODEN: CMCACI. ISSN: 1568-0118. Publisher: Bentham Science Publishers Ltd..

AB . . . the EGFR (Epidermal Growth Factor Receptor). The EGFR family is a group of four structurally similar growth factor receptors with **tyrosine-kinase** activity (EGFR, HER2/neu, **ErbB**-3, **ErbB**-4), which dimerize upon binding with a number of ligands, including EGF (Epidermal Growth Factor) and TGF (Transforming Growth Factor), allowing. . . been associated with a worse clin. outcome. New agents developed to inhibit EGFR function include monoclonal antibodies and small-mol. receptor **tyrosine-kinase** inhibitors. In this review, results of most recent clin. with EGFR inhibitors

including monoclonal antibodies, such as Trastuzumab (Herceptin), IMC-C225 (Cetuximab) and others (ABX-EGF, EMD 72000), and **tyrosine-kinase** inhibitors, such as ZD1839 (Gefitinib, Iressa), OSI-774 (Erlotinib, Tarceva) and others (CI-1033, GW2016), are summarized. In particular, final results of. . .

IT 180288-69-1, Herceptin 183321-74-6, Erlotinib 184475-35-2, Gefitinib 205923-56-4, Cetuximab **289499-45-2**, CI-1033 339177-26-3, ABX-EGF 339186-68-4, EMD 72000 437755-78-7, GW2016
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epidermal growth factor receptor inhibitors in treatment of lung cancer)

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epidermal growth factor receptor inhibitors in treatment of lung cancer)

L3 ANSWER 3 OF 8 MEDLINE on STN

AB The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein that constitutes one of four members of the **erbB** family of **tyrosine kinase** receptors. Binding of EGFR to its cognate ligands leads to autophosphorylation of receptor **tyrosine kinase** and subsequent activation of signal transduction pathways that are involved in regulating cellular proliferation, differentiation, and survival. Although present in normal cells, EGFR is overexpressed in a variety of tumor cell lines and has been associated with poor prognosis and decreased survival. EGFR activation also plays a role in resistance to chemotherapy and radiation treatment in tumor cells. Over the past two decades, much effort has been directed at developing anticancer agents that can interfere with EGFR activity. The most common pharmacologic approaches to inhibiting EGFR have been to develop monoclonal antibodies and small-molecule inhibitors. Monoclonal antibodies block ligand binding to the extracellular domain, whereas the small-molecule inhibitors exert their effects at the intracellular portion of the receptor to prevent **tyrosine kinase** phosphorylation and subsequent activation of signal transduction pathways. A number of EGFR inhibitors have been developed that can arrest tumor growth and, in some cases, cause tumor regression. When used in combination with cytotoxic treatments, chemotherapy, and radiation, EGFR inhibitors have been able to potentiate their anticancer activity.

2004244349. PubMed ID: 15142631. Review of epidermal growth factor receptor biology. Herbst Roy S. (Department of Thoracic Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030-4009, USA.. rherbst@mdanderson.org) . International journal of radiation oncology, biology, physics, (2004) 59 (2 Suppl) 21-6. Ref: 51. Journal code: 7603616. ISSN: 0360-3016. Pub. country: United States. Language: English.

AB The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein that constitutes one of four members of the **erbB** family of **tyrosine kinase** receptors. Binding of EGFR to its cognate ligands leads to autophosphorylation of receptor **tyrosine kinase** and subsequent activation of signal transduction pathways that are involved in regulating cellular proliferation, differentiation, and survival. Although present in. . . to the extracellular domain, whereas the small-molecule inhibitors exert their effects at the intracellular portion of the receptor to prevent **tyrosine kinase** phosphorylation and subsequent activation of signal transduction pathways. A number of EGFR inhibitors

have been developed that can arrest tumor. . .
RN 184475-35-2 (gefitinib); **289499-45-2 (CI1033)**

L3 ANSWER 4 OF 8 MEDLINE on STN DUPLICATE 1
AB Overexpression of **ErbB**-2/HER2 is associated with aggressive human malignancies, and therapeutic strategies targeting the oncoprotein are currently in different stages of clinical application. **Tyrosine kinase** inhibitors (TKIs) that block the nucleotide-binding site of the **kinase** are especially effective against tumors. Here we report an unexpected activity of TKIs: along with inhibition of **tyrosine** phosphorylation, they enhance ubiquitylation and accelerate endocytosis and subsequent intracellular destruction of **ErbB**-2 molecules. Especially potent is an irreversible TKI (CI-1033) that alkylates a cysteine specific to **ErbB** receptors. The degradative pathway stimulated by TKIs appears to be chaperone mediated, and is common to the heat shock protein 90 (Hsp90) antagonist geldanamycin and a stress-induced mechanism. In agreement with this conclusion, CI-1033 and geldanamycin additively inhibit tumor cell growth. Based upon a model for drug-induced degradation of **ErbB**-2, we propose a general strategy for selective destruction of oncoproteins by targeting their interaction with molecular chaperones.
2002328110. PubMed ID: 12006493. Drug-induced ubiquitylation and degradation of **ErbB** receptor **tyrosine kinases** : implications for cancer therapy. Citri Ami; Alroy Iris; Lavi Sara; Rubin Chanan; Xu Wanping; Grammatikakis Nicolas; Patterson Cam; Neckers Len; Fry David W; Yarden Yosef. (Department of Biological Regulation, The Weizmann Institute of Science, Rehovot 76100, Israel.) EMBO journal, (2002 May 15) 21 (10) 2407-17. Journal code: 8208664. ISSN: 0261-4189. Pub. country: England: United Kingdom. Language: English.
TI Drug-induced ubiquitylation and degradation of **ErbB** receptor **tyrosine kinases**: implications for cancer therapy.
AB Overexpression of **ErbB**-2/HER2 is associated with aggressive human malignancies, and therapeutic strategies targeting the oncoprotein are currently in different stages of clinical application. **Tyrosine kinase** inhibitors (TKIs) that block the nucleotide-binding site of the **kinase** are especially effective against tumors. Here we report an unexpected activity of TKIs: along with inhibition of **tyrosine** phosphorylation, they enhance ubiquitylation and accelerate endocytosis and subsequent intracellular destruction of **ErbB**-2 molecules. Especially potent is an irreversible TKI (CI-1033) that alkylates a cysteine specific to **ErbB** receptors. The degradative pathway stimulated by TKIs appears to be chaperone mediated, and is common to the heat shock protein. . . agreement with this conclusion, CI-1033 and geldanamycin additively inhibit tumor cell growth. Based upon a model for drug-induced degradation of **ErbB**-2, we propose a general strategy for selective destruction of oncoproteins by targeting their interaction with molecular chaperones.
RN **289499-45-2 (CI1033)**; 30562-34-6 (geldanamycin)

L3 ANSWER 5 OF 8 MEDLINE on STN
AB Transmembrane receptor **tyrosine kinases** have been shown to play an important role in the modulation of growth factor signaling and regulation of key cellular processes. The **erbB** receptor family is part of the receptor **tyrosine kinase** superfamily and consists of four members, **erbB**-1, **erbB** -2, **erbB**-3, and **erbB**-4. A majority of solid tumors express one or more members of this receptor family, and coexpression of

multiple **erbB** receptors leads to an enhanced transforming potential and worsened prognosis. The **erbB** receptor family has been shown to play an important role in both the development of the normal breast and in the pathogenesis and progression of breast cancer. Receptor overexpression has also been shown to be a negative prognostic indicator and to correlate with both tumor invasiveness and a lack of responsiveness to standard treatment. Clinically, blockade of the **erbB**-2 receptor has recently been shown to provide benefit in a subset of chemotherapy-resistant breast cancer patients. CI-1033 is an orally available pan-**erbB** receptor **tyrosine kinase** inhibitor that, unlike the majority of receptor inhibitors, effectively blocks signal transduction through all four members of the **erbB** family. In addition, it blocks the highly tumorigenic, constitutively activated variant of **erbB**-1, EGFRvIII, and inhibits downstream signaling through both the Ras/MAP **kinase**, and PI-3 **kinase**/AKT pathways. CI-1033 is also unique in that it is an irreversible inhibitor, thereby providing prolonged suppression of **erbB** receptor-mediated signaling. Preclinical data have shown CI-1033 to be efficacious against a variety of human tumors in mouse xenograft models, including breast carcinomas. In a phase I study, CI-1033 has been shown to have an acceptable side effect profile at potentially therapeutic dose levels and demonstrates evidence of target biomarker modulation. Antitumor activity has also been observed in this study, including one partial clinical response and stable disease in over 30% of patients, including one patient with heavily pretreated breast cancer. By virtue of its pan-**erbB** receptor inhibition and potent interruption of downstream mitogenic signaling pathways, CI-1033 may have clinical activity for solid tumors that overexpress one **erbB** family member, coexpress multiple members of the **erbB** family, or express a constitutively activated, mutated form of these receptors. Given the important role of the **erbB** receptor family in the pathogenesis and progression of breast cancer, an irreversible pan-**erbB** inhibitor like CI-1033 could have an important role to play in the future treatment of breast cancer.

2002389796. PubMed ID: 12138393. Potential benefits of the irreversible pan-erbB inhibitor, CI-1033, in the treatment of breast cancer. Allen Lee F; Lenehan Peter F; Eiseman Irene A; Elliott William L; Fry David W. (Departments of Clinical Development, Oncology, and Cancer Pharmacology, Pfizer Global Research and Development, Ann Arbor Laboratories, Ann Arbor, MI 48105, USA.) Seminars in oncology, (2002 Jun) 29 (3 Suppl 11) 11-21. Ref: 108. Journal code: 0420432. ISSN: 0093-7754. Pub. country: United States. Language: English.

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RN **289499-45-2 (CI1033)**

L3 ANSWER 6 OF 8 MEDLINE on STN

AB The **ErbB** receptor family is implicated in the malignant transformation of several tumor types and is overexpressed frequently in breast, ovarian, and other tumors. The mechanism by which CI-1033 and gemcitabine, either singly or in combination, kill tumor cells was examined in two breast lines, MDA-MB-453 and BT474; both overexpress the **ErbB**-2 receptor. CI-1033, a potent inhibitor of the **ErbB** family of receptor **tyrosine kinases**, reduced levels of activated Akt in MDA-MB-453 cells. This effect alone, however, did not induce apoptosis in these cells. Gemcitabine treatment resulted in a moderate increase in the percentage of apoptotic cells that was accompanied by activation of p38 and MAPK (ERK1/2). CI-1033 given 24 h after gemcitabine produced a significant increase in the apoptotic fraction over treatment with either drug alone. During the combined treatment p38 remained activated, whereas Akt and activated MAPK were suppressed. Substitution of CI-1033 with the phosphatidylinositol 3-**kinase** inhibitor LY294002 and the MAPK/ERK **kinase** inhibitor PD 098059 in combination with gemcitabine produced the same results as the combination of CI-1033 and gemcitabine. p38 suppression by SB203580 prevented the enhanced cell kill by CI-1033. In contrast to MDA-MB-453, BT474 cells exhibited activated p38 under unstressed conditions as well as activated Akt and MAPK. Treatment of BT474 cells with CI-1033 inhibited both the phosphorylation of Akt and MAPK and resulted in a 47% apoptotic fraction. Gemcitabine did not cause apoptosis in the BT474 cells. These data indicate that suppression of Akt and MAPK in the presence of activated p38 results in cell death and a possible mechanism for the enhanced apoptosis produced by the combination of CI-1033 and gemcitabine in MDA-MB-453 cells. Furthermore, tumors that depend on **ErbB** receptor signaling for survival and exhibit activated p38 in the basal state may be susceptible to apoptosis by CI-1033 as a single agent.

2001370796. PubMed ID: 11278435. Akt, MAPK (Erk1/2), and p38 act in concert to promote apoptosis in response to ErbB receptor family inhibition. Nelson J M; Fry D W. (Pfizer Global Research and Development, Ann Arbor, Michigan 48105, USA.. James.Nelson@Pfizer.com) . Journal of biological chemistry, (2001 May 4) 276 (18) 14842-7. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

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RN 103882-84-4 (gemcitabine); 154447-36-6 (2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one); **289499-45-2 (CI1033)**; 951-77-9 (Deoxycytidine)

L3 ANSWER 7 OF 8 MEDLINE on STN DUPLICATE 2

AB Overexpression of the **erbB** family of receptor **tyrosine kinases** has been implicated in a variety of tumors including breast, lung, prostate, and brain. Most solid tumors express one or more of these receptors, which can often be related to tumor aggressiveness and poor patient prognosis. CI-1033, a pan-**erbB tyrosine kinase** inhibitor, is a clinically promising agent that is active against all four members of the **erbB** receptor **tyrosine kinase** family. In vitro studies of human cancer cell lines indicate that CI-1033 results in prompt, potent, and sustained inhibition of **tyrosine kinase** activity. This inhibition is highly selective for erbB1 (epidermal growth factor receptor), erbB2, erbB3, and erbB4 without inhibiting **tyrosine kinase** activity of receptors such as platelet-derived growth factor receptor, fibroblast growth factor receptor, and insulin receptor, even at high concentrations. Treatment of athymic nude mice bearing xenografts of human A431 epidermoid carcinoma, H125 non-small cell lung carcinoma, and SF-767 glioblastoma results in highly significant suppression of tumor growth. The major toxicity in animals is diarrhea, which is more severe at higher doses. In animal models, all side effects are reversible on cessation of treatment. Thus, CI-1033, which is currently undergoing phase I clinical trials, holds significant potential for use in a broad range of solid tumors.

2001653491. PubMed ID: 11706399. CI-1033, a pan-**erbB tyrosine kinase** inhibitor. Slichenmyer W J; Elliott W L; Fry D W. (Department of Cancer Research, Pfizer Global Research and Development, Ann Arbor, MI 48105, USA.) Seminars in oncology, (2001 Oct) 28 (5 Suppl 16) 80-5. Ref: 19. Journal code: 0420432. ISSN: 0093-7754. Pub. country: United States. Language: English.

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RN **289499-45-2 (CI1033)**

L3 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AB Several agents that target one or more members of the **erbB** family of receptor **tyrosine kinases** are currently undergoing clin. investigation. The monoclonal antibody trastuzumab has been shown effective in erbB2-expressing metastatic breast cancer when administered as a single agent or in combination with cytotoxic chemotherapy. Toxicities associated with trastuzumab include infusion-related fever and chills, hypersensitivity reactions, and congestive heart failure. C225 is a monoclonal antibody directed against the epidermal growth factor receptor, which has shown encouraging antitumor activity in early clin. development. The orally active **tyrosine kinase** inhibitors show encouraging antitumor activity in preclin. models and early clin. trials. Members of this class currently in clin. development include ZD1839, OSI774, and CI-1033. Evidence to data suggests that the major role for **erbB** receptor-targeting drugs will be in combined therapy to enhance response to cytotoxic drugs, and in long-term monotherapy to maintain response and prevent disease progression or recurrence.

2001:921398 Document Number 137:87979 Anticancer therapy targeting the **ErbB** family of receptor **tyrosine kinases**.
Slichenmyer, William J.; Fry, David W. (Departments of Oncology Clinical Development and Cancer Research, Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA). Seminars in Oncology, 28(5, Suppl. 16), 67-79 (English) 2001. CODEN: SOLGAV. ISSN: 0093-7754. Publisher: W. B. Saunders Co..

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ST anticancer therapy **ErbB** receptor **tyrosine kinase**

IT Antitumor agents
Human
(anticancer therapy targeting the **ErbB** family of receptor **tyrosine kinases**)

IT Epidermal growth factor receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(anticancer therapy targeting the **ErbB** family of receptor **tyrosine kinases**)

IT Antitumor agents
(breast cancer metastasis; anticancer therapy targeting the **ErbB** family of receptor **tyrosine kinases**)

IT Mammary gland, neoplasm
(metastasis; anticancer therapy targeting the **ErbB** family of receptor **tyrosine kinases**)

IT 340830-03-7, Receptor **tyrosine kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(anticancer therapy targeting the **ErbB** family of receptor **tyrosine kinases**)

IT 180288-69-1, Trastuzumab 183319-69-9, OSI774 184475-35-2, ZD1839
205923-56-4, C225 **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticancer therapy targeting the **ErbB** family of receptor **tyrosine kinases**)

IT 80449-02-1, Protein **tyrosine kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; anticancer therapy targeting the **ErbB** family of receptor **tyrosine kinases**)

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticancer therapy targeting the **ErbB** family of receptor **tyrosine kinases**)